



# Menopause

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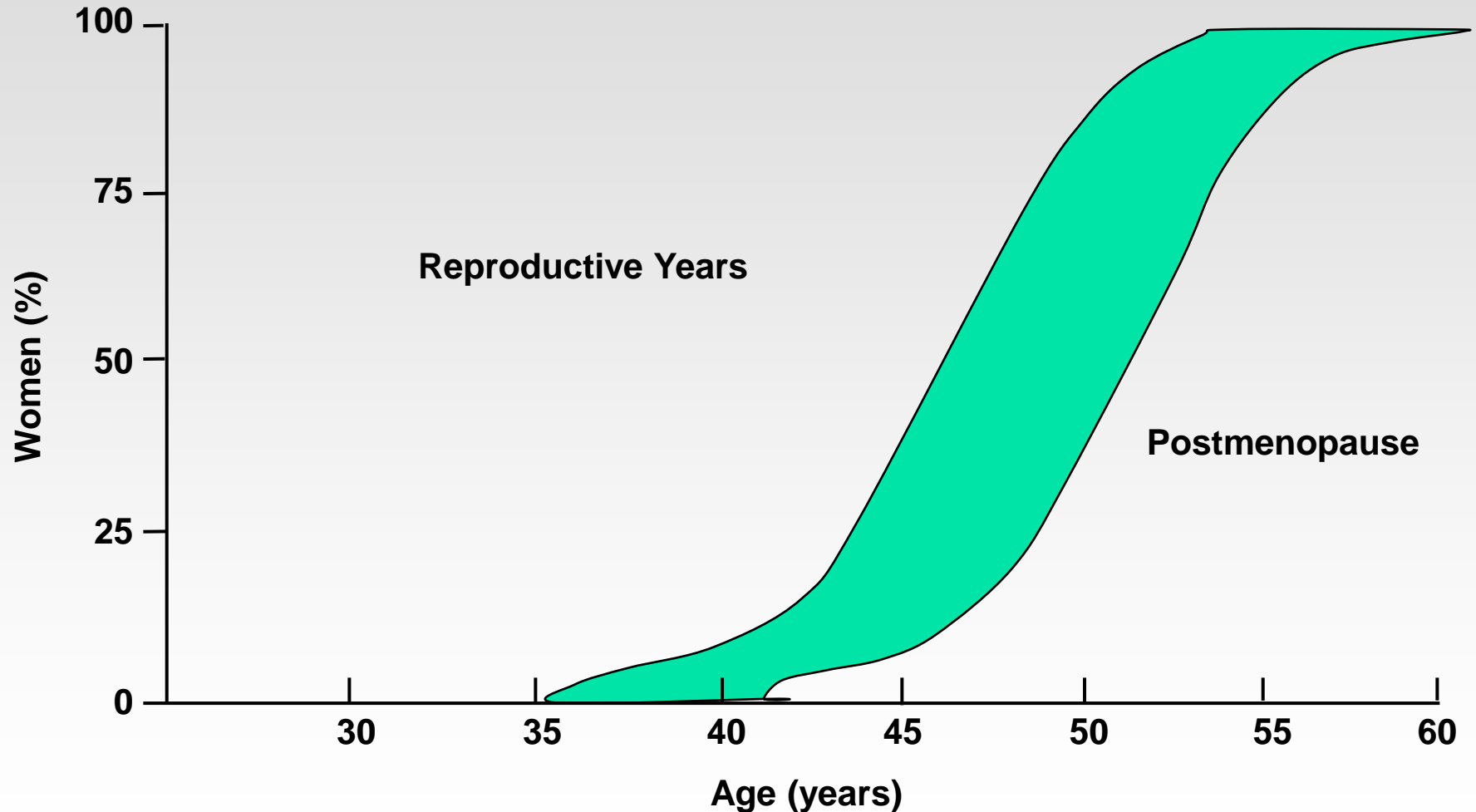
# Menopause Basics

- By 2010, 45% of American women will be over age 50

# Changes Prior to Menopause

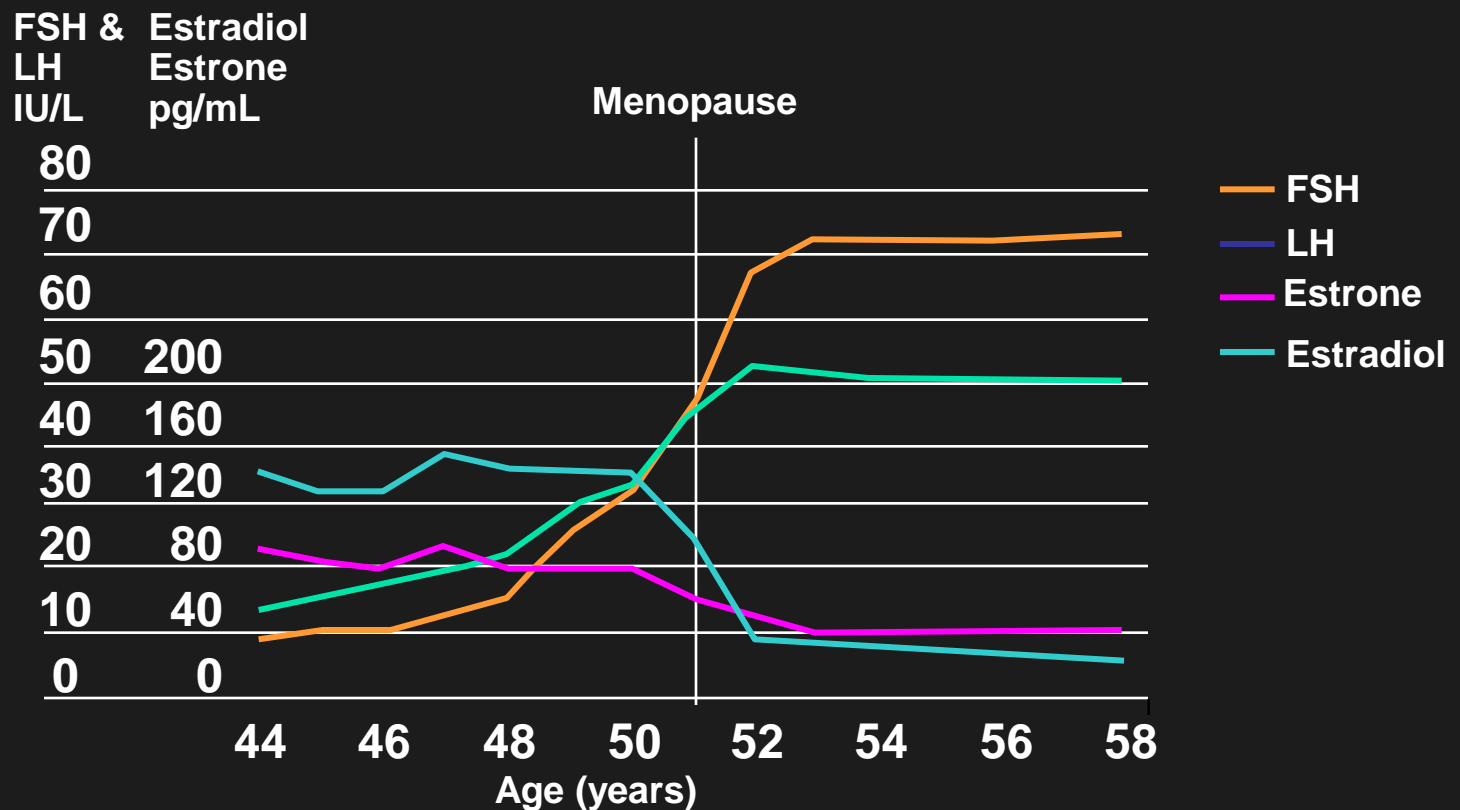
- ↑ Anovulatory cycles
- ↑ or ↓ Menstrual cycle length
- ↑ FSH level (day 3)
- ↓ Inhibin B

# Perimenopausal Transition Years



# Endocrine Changes

## Mean Circulating Hormone Levels



# Serum Concentrations of Ovarian Hormones

	Premenopause (mean)	Postmenopause (mean)
Estradiol (pg/mL)	50-400	8-35 (<25)
Estrone (pg/mL)	30-300	20-60
Testosterone (ng/dL)	20-50 (35)	30
Androstenedione (ng/dL)	~130	~50

Ovaries produce more androgen than estrogen.

# Changes — Declining Estrogen

- Hot flushes
- Urogenital atrophy
- Mood changes
- Changes in cognitive function
- Bone loss
- Changes in skin appearance
- Increase in risk of cardiovascular disease
- Physiologic changes of the eye

# Menstrual Cycle Changes

Hallmark of perimenopause — menstrual changes

- Usually shorter cycle length (eg, by 2 to 7 days)
  - longer or irregular less common
- Changes in quality
  - Heavier initially, then lighter
  - Spotting prior to menses



# Vasomotor Instability

- “Hot flashes are one of the chief menopausal complaints for which women in Western societies seek medical treatment.”
- ~ 85% of perimenopausal women experience vasomotor instability — hot flashes, night sweats, sleep disturbances
- Intensity, duration, and frequency highly variable: 1-2 to 40 flushes/day

# Hot Flash Rates

Menstrual Status	% Reporting Hot Flashes
Premenopausal*	~10%
Perimenopausal†	~30% to 85%
Recently postmenopausal	~20% to 90%
4 years postmenopause	~20% to 60%

\*Menstruation within the 3 prior months with no change in regularity of cycle.

†3 to 11 months of amenorrhea or increased menstrual irregularity.

1. McKinlay SM et al. *Maturitas*. 1992;14:103-115.
2. Kronenberg F. *Ann N Y Acad Sci*. 1990;592:52-86.
3. Nachtigall LE. *Clin Obstet Gynecol*. 1998;41:921-927

# Age of Menopause

Median age of natural menopause (y)<sup>1,2</sup>

Overall 51.1-51.4

Smokers 1 to 2 years younger

Likelihood of being menopausal by<sup>1,2</sup>

Age 50 y ~30%

Age 55 y\* >80%

\*May be more appropriate than age 50 for OC discontinuation.

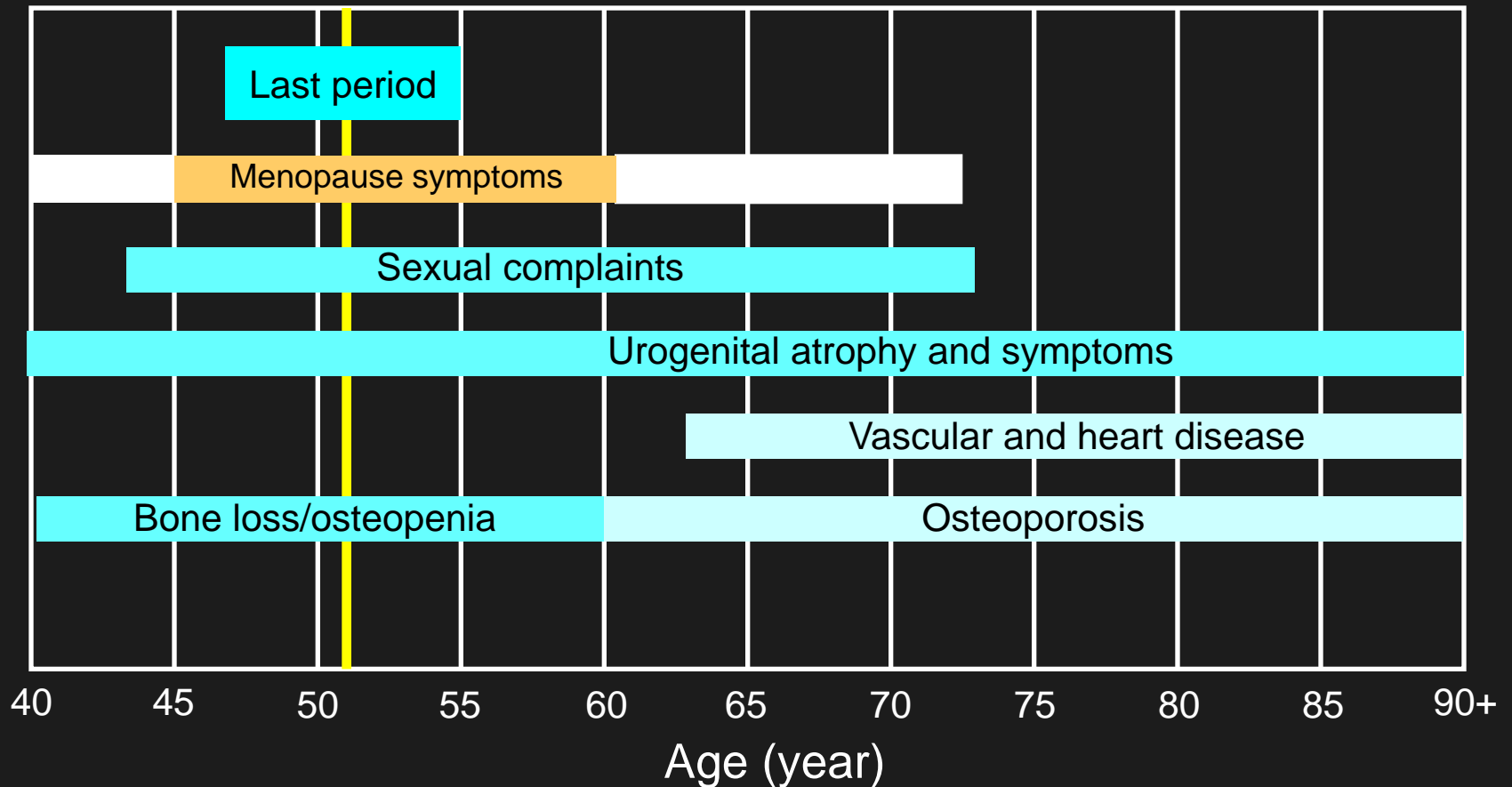
1. Stanford JL et al. *J Chron Dis*. 1987;40:995-1002.

2. McKinlay SM et al. *Ann Intern Med*. 1985;103:350-356.

# The Menopausal Syndrome

- Hot flushes/night sweats
- Palpitations
- Sleep disturbance
- Chest pressure
- Shortness of breath
- Headaches
- Numbness
- Fatigue
- Weakness
- Joint pain
- Decreased sexual desire
- Vaginal dryness and painful intercourse
- Loss of urinary control
- Memory loss
- Anxiety
- Depression

# Hormone Deficiency Effects



# Genitourinary Symptoms Associated With Menopause

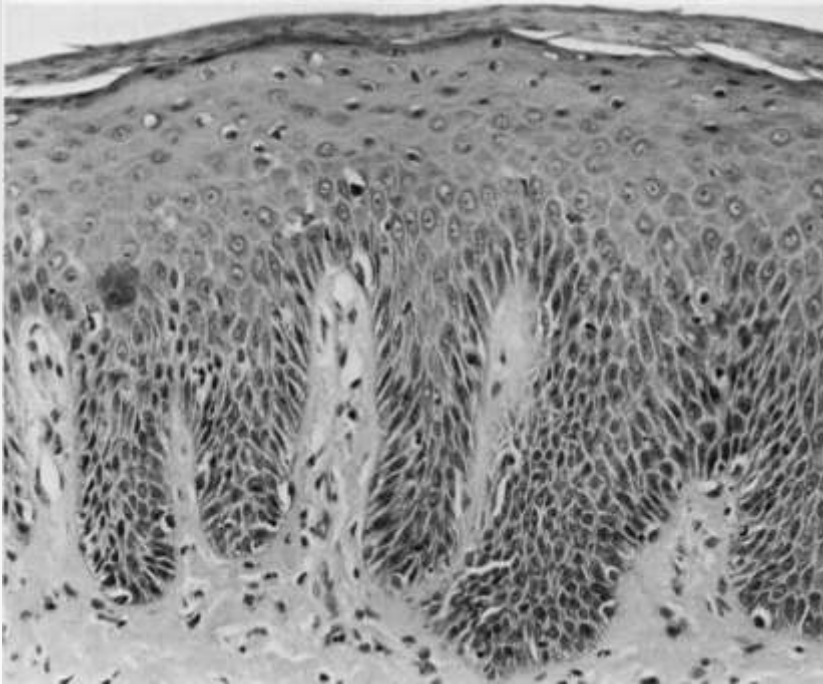
## Genital

- ⑩ Irritation, burning, pruritus
- ⑩ Leukorrhea
- ⑩ Dyspareunia
- ⑩ Decreased vaginal secretions
- ⑩ Shortening/lessening of vaginal distensibility

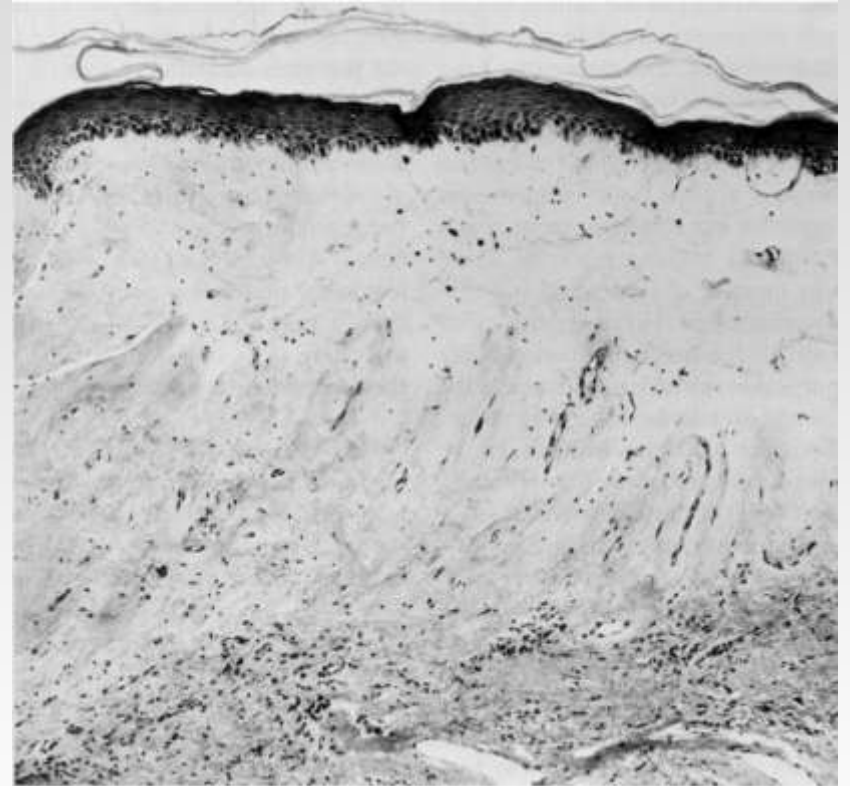
## Urinary

- ⑩ Frequency, urgency
- ⑩ Dysuria
- ⑩ Nocturia
- ⑩ Incontinence\*

# Vaginal Cytology



Premenopause



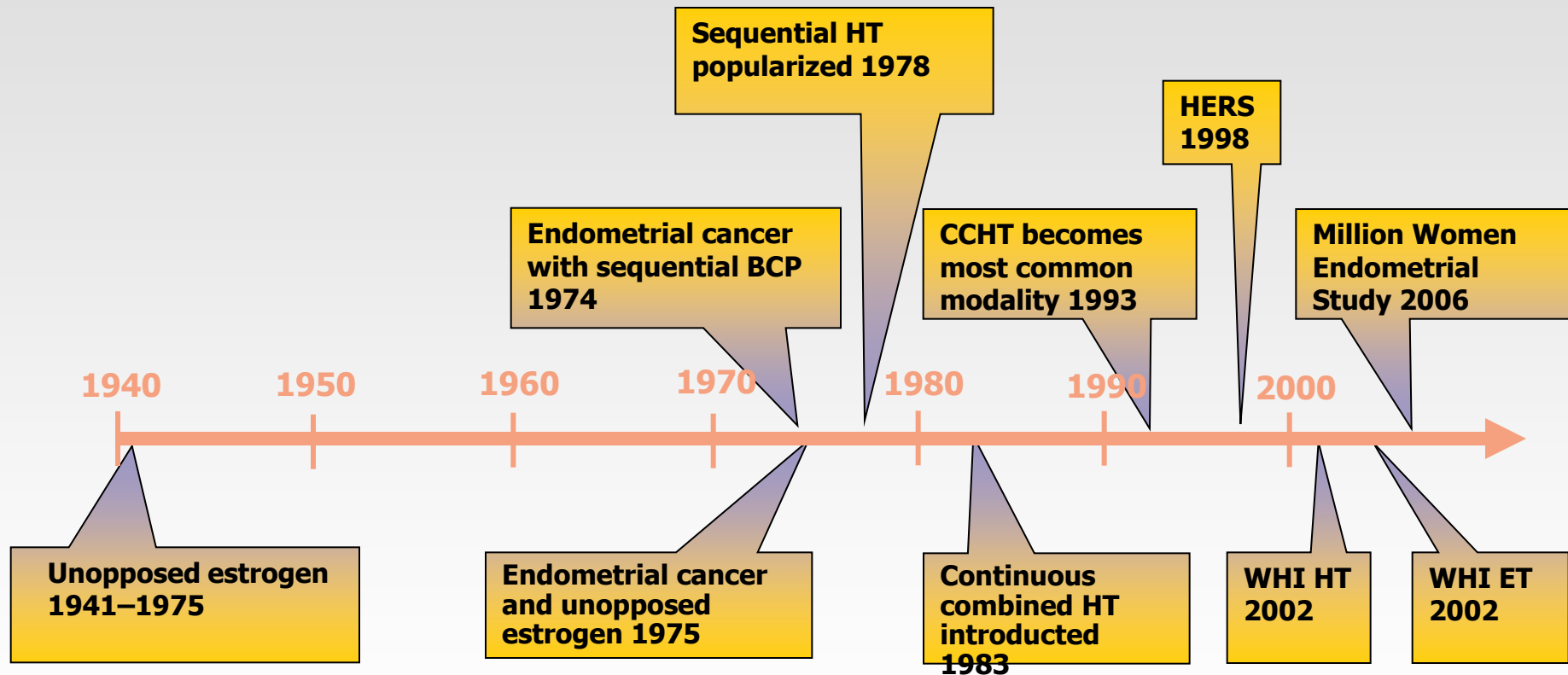
Postmenopause

Putting the Risks into Perspective

# **HISTORY OF HT USE**



# Milestones in Hormone Therapy (HT): 1940–2000



\* PEPI = Postmenopausal Estrogen/Progestin Interventions trial

\* HOPE = Health, Osteoporosis, Progestin/Estrogen study

# Observational Trial Results

- 1976: Lowers risk of osteoporosis
- 1981: CHD benefit, inconclusive for stroke
- 1988: Reduction in mortality
- 1994: Reduction in Alzheimer's risk
- Accelerated use of hormone therapy

# Randomized Controlled Trial Results

- 1998: HERS found that HT does not prevent CHD
- Mid-2002: WHI found that HT does not help CHD and may increase CHD and breast cancer risk

# Heart and Estrogen/Progestin Replacement Study (HERS)

- Conducted to determine if older women with heart disease have CVD protection with HT
- Studied postmenopausal women (mean age, 67 years)
- Used EPT for 4.1 years

# HERS Conclusions

- Older women with pre-existing disease had increased CVD risk
- Risk was observed early in treatment

# European Trials

- One (HABITS) with continuous E+P showed  $>$  BCA recurrence risk
- Other (Scandinavian trial) with ET and only intermittent P, showed  $18\% <$  BCA recurrence risk

# Osteoporotic Fracture Risk

## Observational data

- Relative risk = 0.6 (40% decreased risk)

## RCT data (WHI) for both EPT and ET

- Relative risk = 0.60-0.70 (30% to 40% decreased risk)
- Absolute risk of hip fracture = 5-6 fewer fractures per 10,000 women per year of HT use
- Absolute risk of total fracture = 44-56 fewer fractures per 10,000 women per year of HT use

ET = CE; EPT = CE + MPA

# Women's Health Initiative (WHI)

- Conducted to determine if “healthy” women have CHD protection with HT
- Studied 161,808 women aged 50-79 years
- Used EPT or ET for 5 to 7 years
- Conclusions:
  - No CHD benefit with HT
  - Perceived VTE and breast cancer risks



# WHI Limitations

- Only one estrogen was used (CEE, alone and with MPA)
- Only one route of administration was used (oral)
- Subjects were:
  - Older (mean age, 63 years)
  - Most more than 10 years beyond menopause
  - Had more risk factors than younger women who typically use HT for menopausal symptoms
  - Largely asymptomatic

# More Recent WHI Analyses of Younger Women (50-59 years)

- 7% decrease in CHD with ET or EPT (2 fewer cases per 10,000 per year of use)
- 24% increase in breast cancer with EPT (9 more cases per 10,000 per year of use)
- 20% decrease in breast cancer with ET (7 fewer cases per 10,000 per year of use)
- 30% decrease in total mortality with ET or EPT (10 fewer deaths per 10,000 per year of use)

ET = CE; EPT = CE + MPA

# WHI Summary

Effects per 10,000 women/year of ET use (ages 50-59)

- 10 fewer deaths
- 10 fewer CHD events
- 2 fewer strokes
- 4 additional VTE

Effects per 10,000 women/year of EPT use (<10 years postmenopause)

- 6 fewer deaths
- 4 fewer CHD events
- 5 more strokes
- 11 additional VTE

# WHI and Breast Cancer Risk

## With EPT use

- Relative risk = 1.24 (24% increased risk)
- Absolute risk = 9 more cancers per 10,000 women per year of EPT use

## With ET use

- Relative risk = 0.80 (20% decreased risk)
- Absolute risk = 7 fewer cancers per 10,000 women per year of ET use
- 33% statistically significant decreased risk when adherent to treatment (i.e., used ET 80% of the time)

ET = CE; EPT = CE + MPA

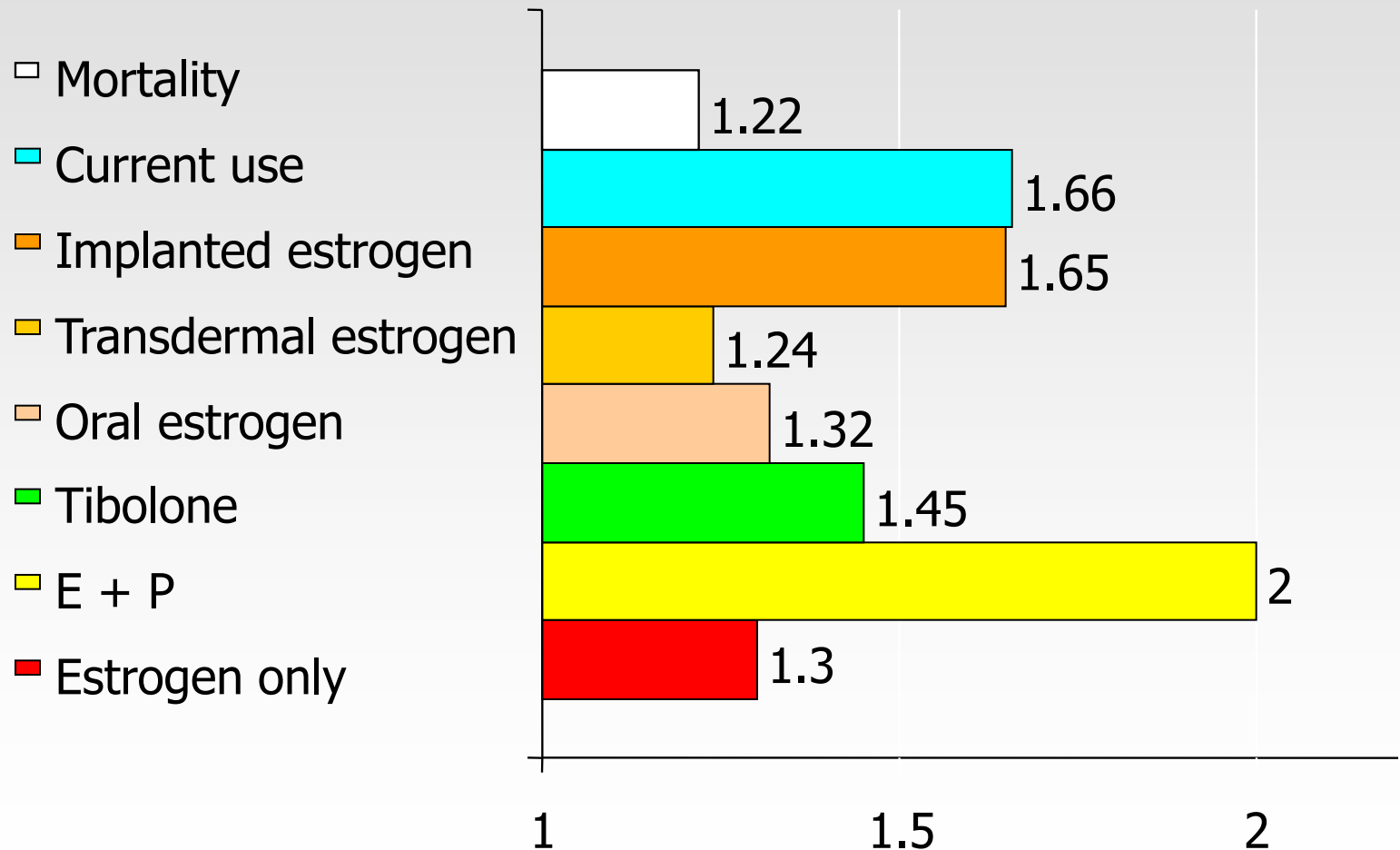
# Million Women Study

- ⑩ 1,091,250 UK women
- ⑩ aged 50-64 years
- ⑩ Half had used menopausal hormone therapy (HT)
  - including ever-users, past users, current users
- ⑩ Type of hormones
  - oestrogen only 41%
  - oestrogen-progestagen 50%
  - tibolone 6%
  - other 1%
  - unknown 2%



MPA	23,908 (18%)
NETA	52,508
LNG or NG	59,346
TOTAL	134,760

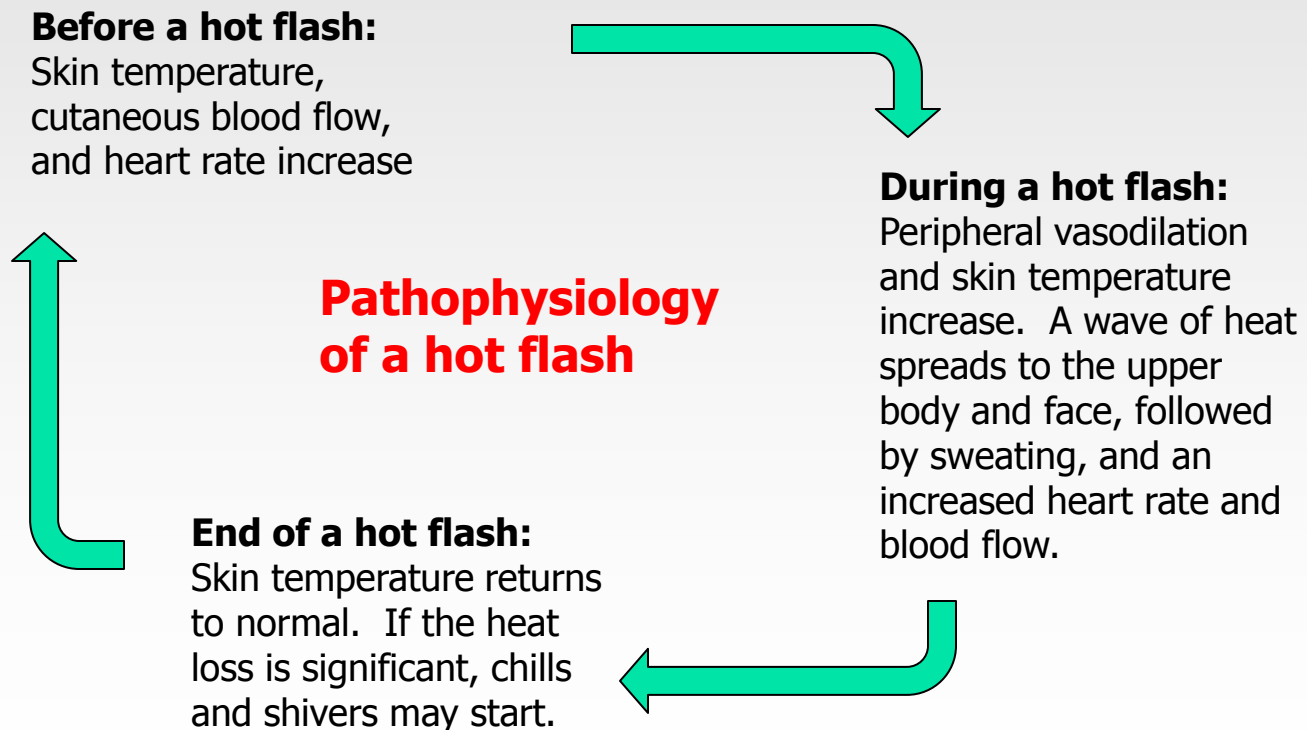
# Million Women Study: Breast Cancer Relative Risks



# **VASOMOTOR SYMPTOMS**

# Pathophysiology of a Hot Flash

Caused by altered peripheral thermoregulators, hypothalamic core temperature dysregulation, or central neurochemical imbalances caused by increased gonadotropins.





# Treatment of mild vasomotor symptoms~

- First consider lifestyle changes alone
- Add nonprescription remedy, such as:
  - dietary isoflavones
  - black cohosh or vitamin E
- Although insufficient clinical trial evidence to support efficacy of these options
- But they are reasonable approaches given lack of potential short-term adverse effects
- It is not known whether isoflavone supplements can be safely consumed by women with breast cancer

# Treatment of moderate to severe vasomotor symptoms

- Prescription systemic hormone therapy, either as combined estrogen-progestogen therapy (EPT) or estrogen (ET) for women after hysterectomy, remains the gold standard for treatment in women without contraindications
- Oral contraceptives are an option for perimenopausal women, especially those needing contraception

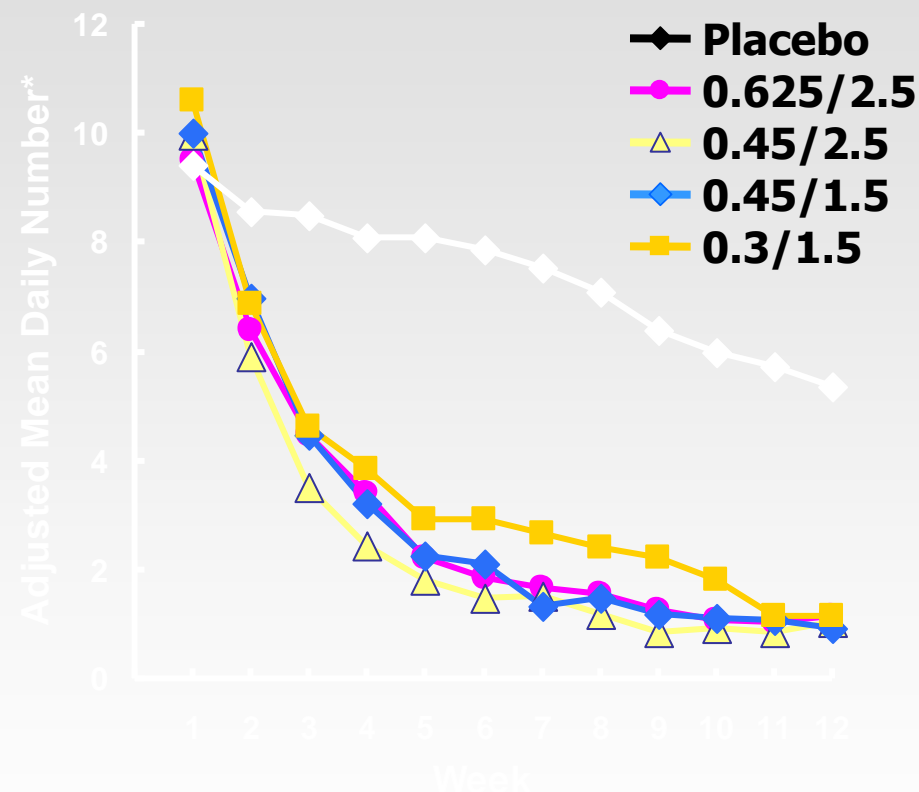
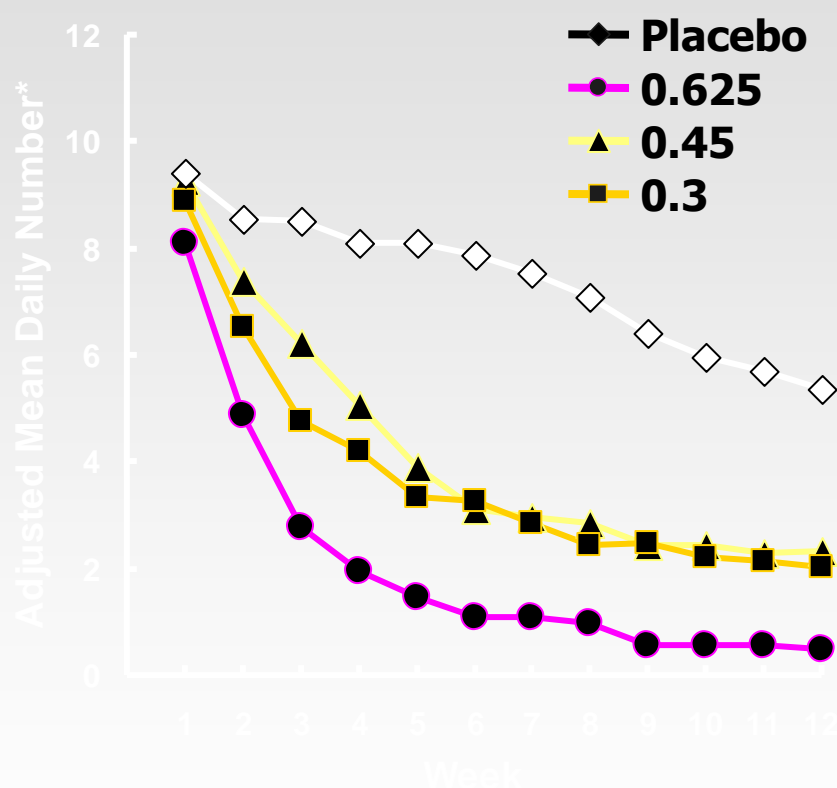
# Treatment of moderate to severe vasomotor symptoms (cont'd)

Options for women with concerns relating to estrogen-containing treatments include lifestyle modification combined with one of the following, provided there are no contraindications:

- The antidepressants venlafaxine, paroxetine, or fluoxetine
- Gabapentin
- Progestogens, although no definitive data are available on long-term safety in women with a history of breast cancer
- Clonidine or methyldopa, but they are limited by only moderate efficacy combined with a relatively high rate of adverse events

# Women's HOPE Study

*Change in Number of Hot Flashes Over 12 Weeks*  
( $n = 241$ )



\*Adjusted for baseline.

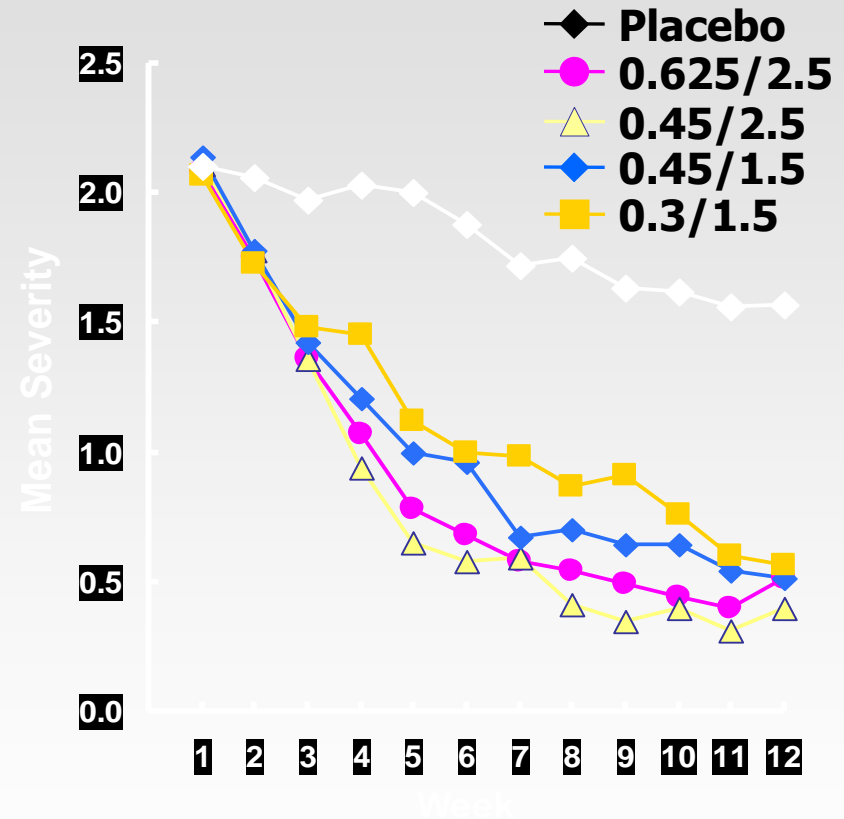
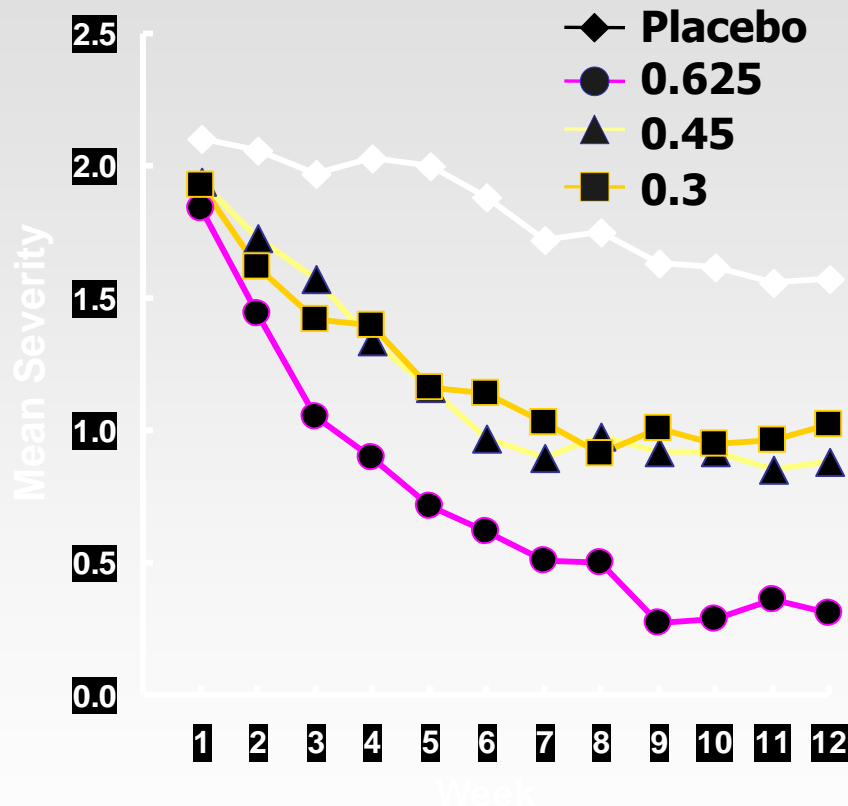
Mean hot flashes at baseline = 12.3 (range 11.3–13.8).

Analyses included women who recorded taking study medication and had at least 7 moderate-to-severe flushes/week or at least 50 flushes per week at baseline.

Utian WH, et al. *Fertil Steril*. 2001;75:1065-79. Used with permission.

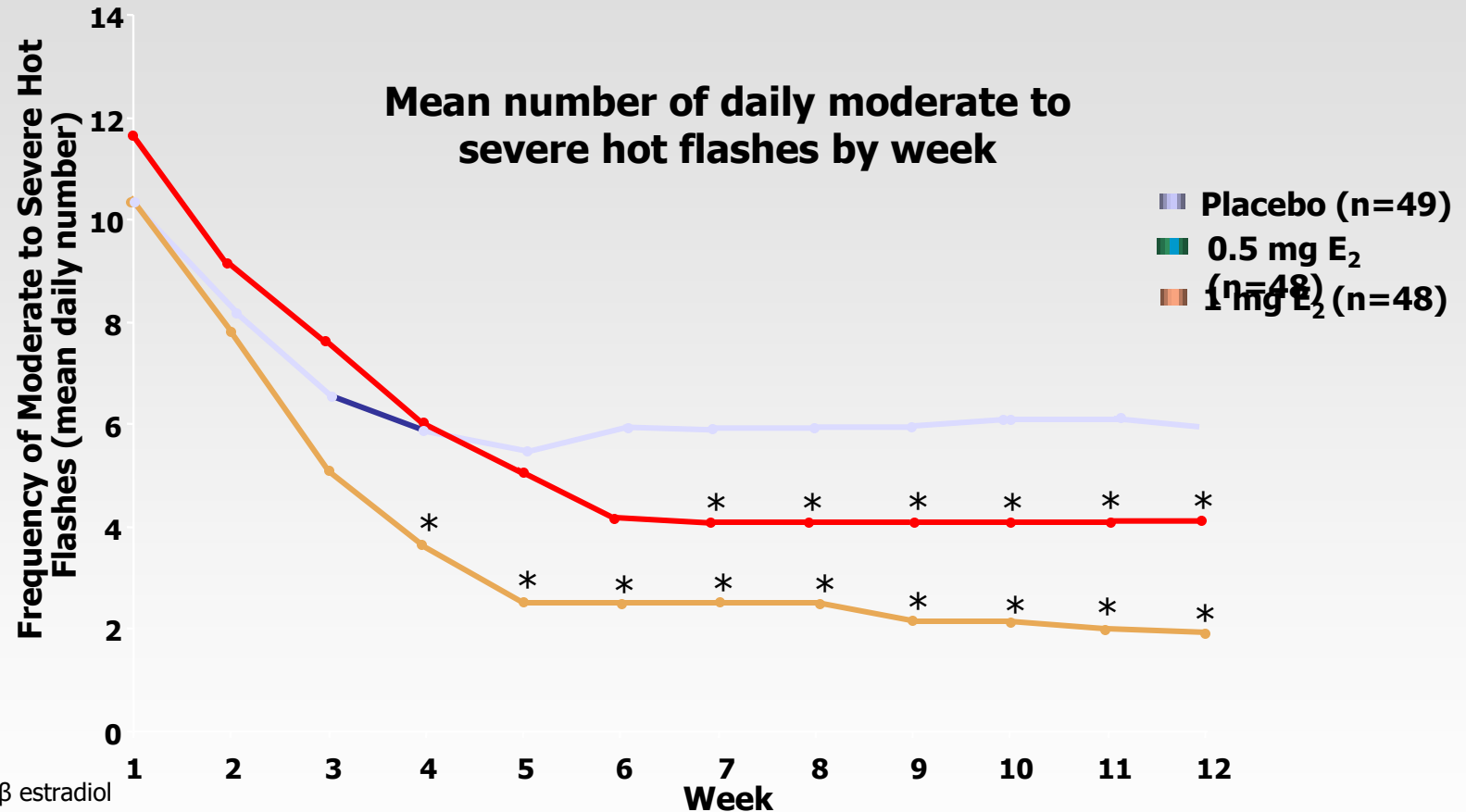
# Women's HOPE Study

## *Changes in Severity of Hot Flashes Over 12 Weeks* (*n* = 241)



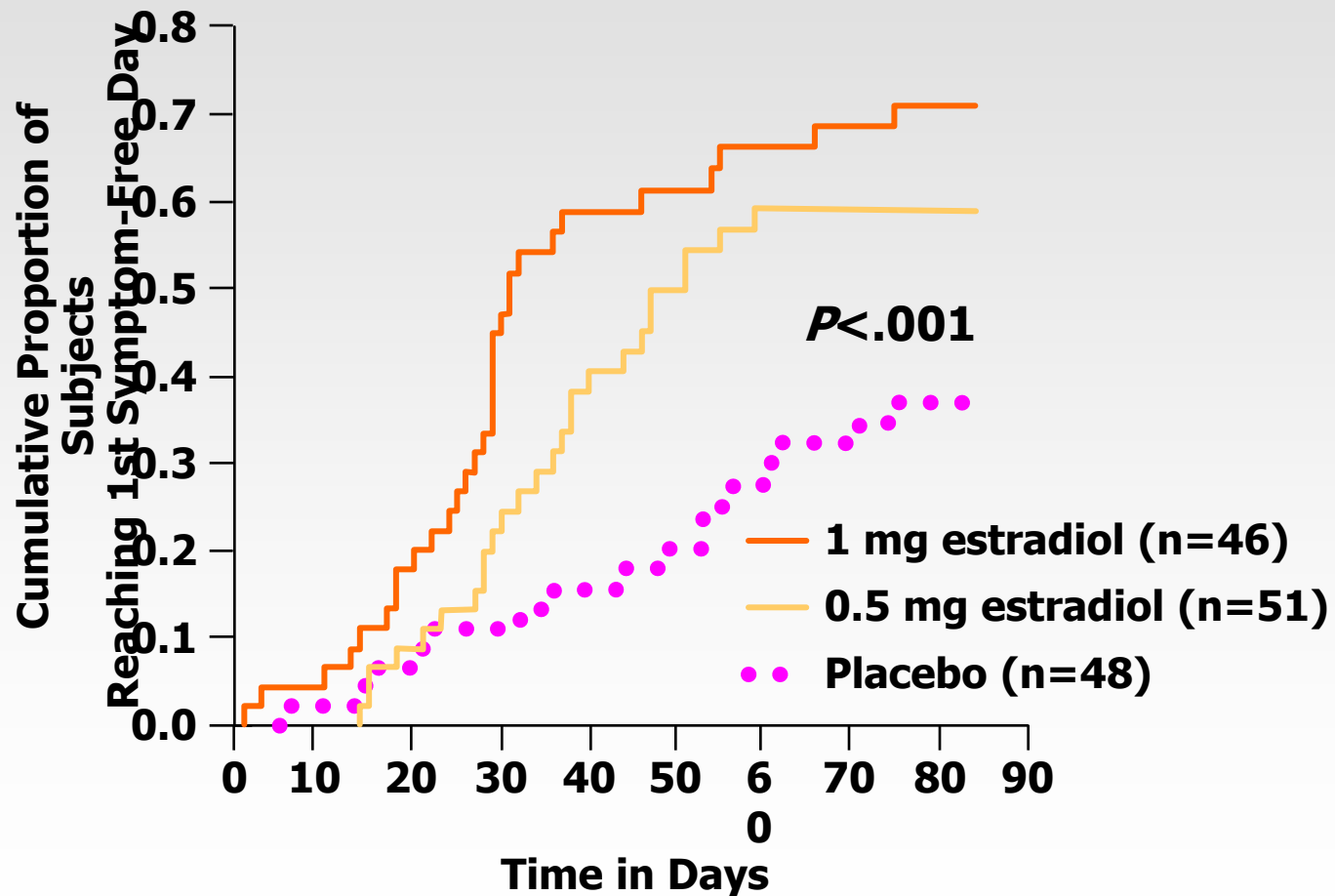
Hot flush severity: 1 = mild, 2 = moderate, 3 = severe. Mean hot flush severity at baseline = 2.3 (range 2.2–2.4).  
 EE = Efficacy-evaluable population included women who recorded taking study medication and had at least 7 moderate-to-severe flushes/week or at least 50 flushes per week at baseline.  
 Utian WH, et al. *Fertil Steril*. 2001;75:1065-79. Used with permission.

# 17- $\beta$ Estradiol Significantly Reduces Vasomotor Symptoms in 4 Weeks



# Estradiol Dose and First Symptom Free Day

## Cumulative Proportion of Subjects Reaching the First Symptom-Free Day



# Estrogens and VMF

- ⑩ Higher doses are associated with higher rates of response
- ⑩ Higher doses are associated with more rapid response
- ⑩ Response depends on bioavailability and reaching adequate serum-tissue-receptor levels
- ⑩ **BOTTOM LINE:** More is better



# Non-hormonal Therapies

- Herbal therapy — black cohosh, St. John's wort
- Biologically based substances — phytoestrogens: isoflavones from soy protein, or red clover
- Lifestyle modifications — relaxation, paced respiration, moderate physical activity

# Non-hormonal — Summary

- For women who prefer non-hormonal pharmacotherapies, and for those who are contraindicated for hormones, venlafaxine, paroxetine, fluoxetine, and gabapentin many offer relief from vasomotor symptoms.
- The efficacy of these agents is modest, compared to estrogen-based therapy.
- A number of over-the-counter plant/herbal remedies, lifestyle modifications, and coping strategies have shown some positive results.

# Management during treatment

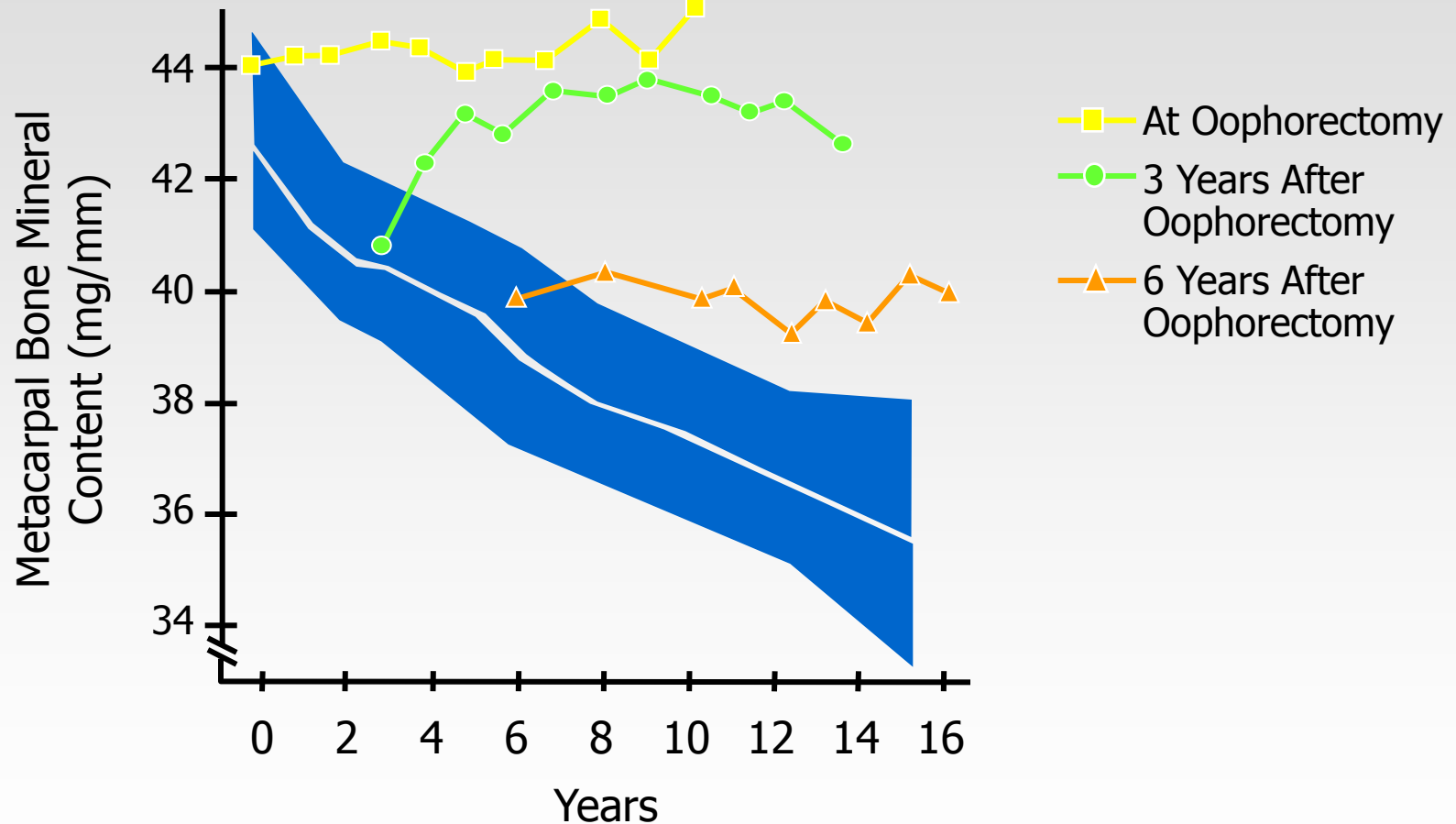
- Regardless of management option utilized, treatment should be periodically evaluated to determine if it is still necessary
- In almost all women, menopause-related vasomotor symptoms will abate over time without any intervention



# Estrogens and VVA

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# Effect of Delayed Initiation of HT on Bone Loss



Blue area represents placebo-treated population of oophorectomized women.  
Lindsay R, et al. *Lancet*. 1976;1:1038-41.

# Study of Osteoporotic Fractures (SOF)

- ⑩ Prospective; 9,704 women  $\geq$  age 65
  - 4 urban communities in the US
- ⑩ Baseline exam
  - BMD, risk factors, cognitive tests
  - Serum archived at  $-190^{\circ}\text{C}$
- ⑩ Follow-up for  $> 12$  years
  - X-ray-validated fractures
  - Strokes, breast cancer confirmed by records

# Long-term HRT is associated with decreased fracture risk

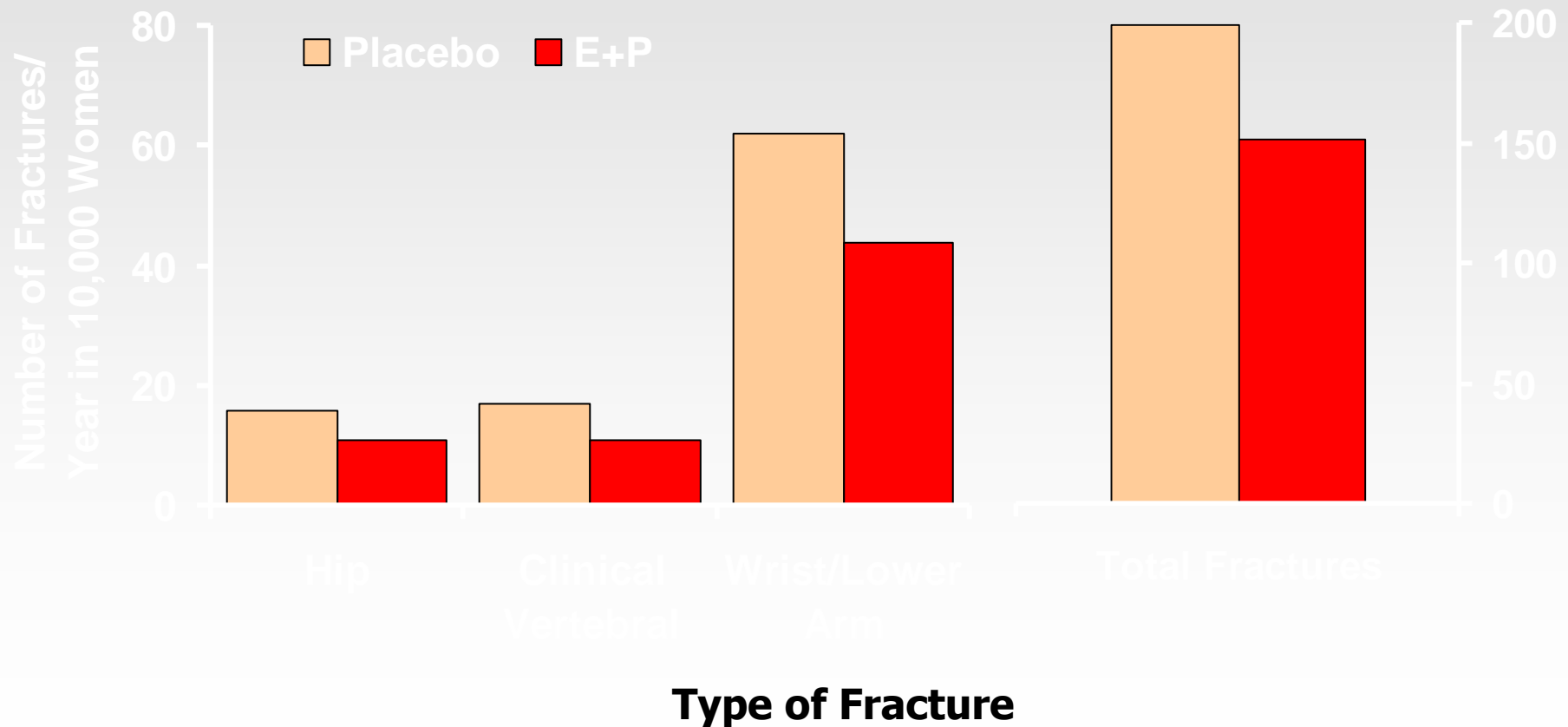
*Current users*

<u>Fractures</u>	<u>&lt; 10 yrs</u>	<u>&gt; 10 yrs</u>
Hip	0.8	0.3*
All non-spine	0.7*	0.6*

\*  $p < 0.05$

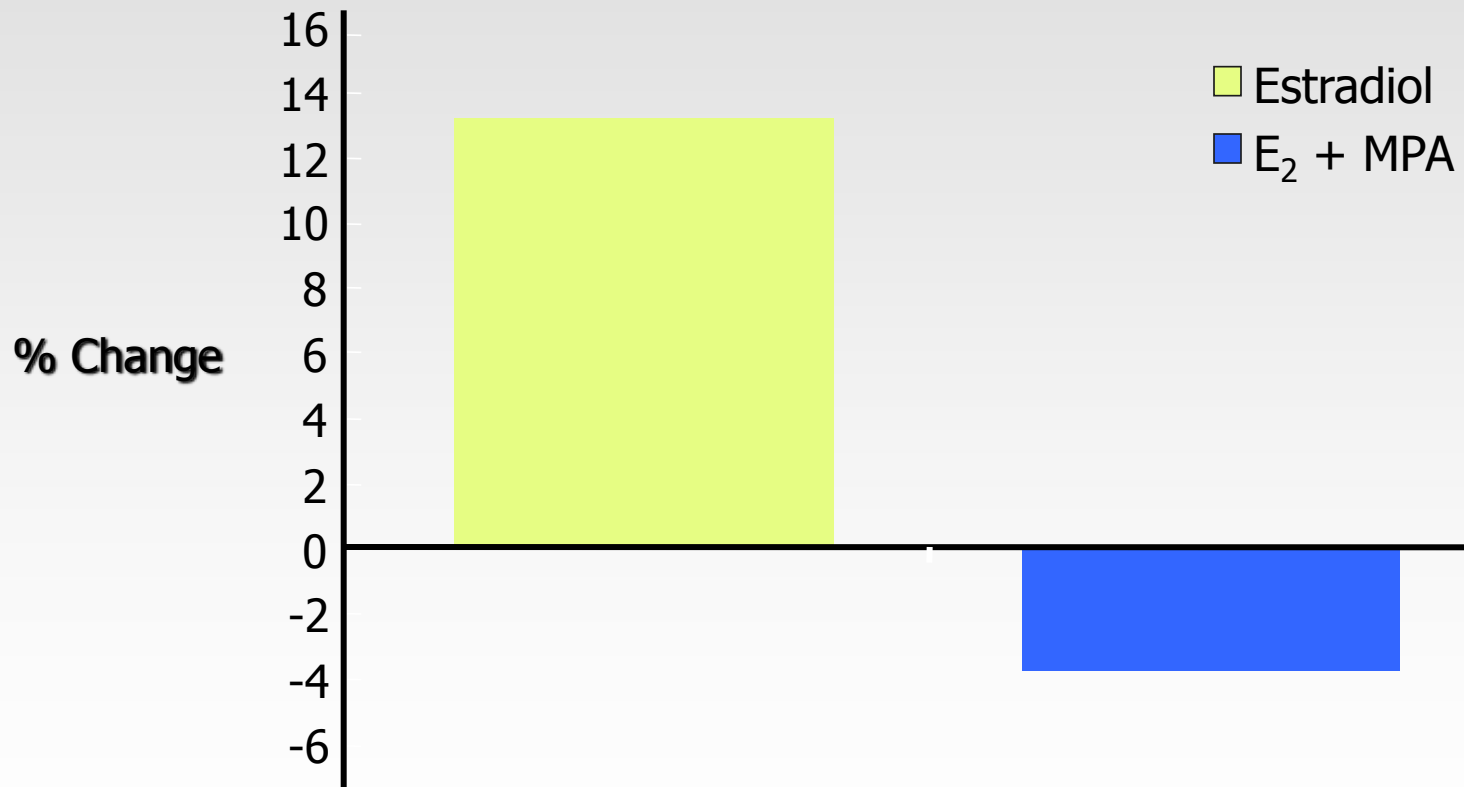
# WHI Results: Effect of E+P in Preventing Fractures

## *Number of Fractures/Year in 10,000 Women*



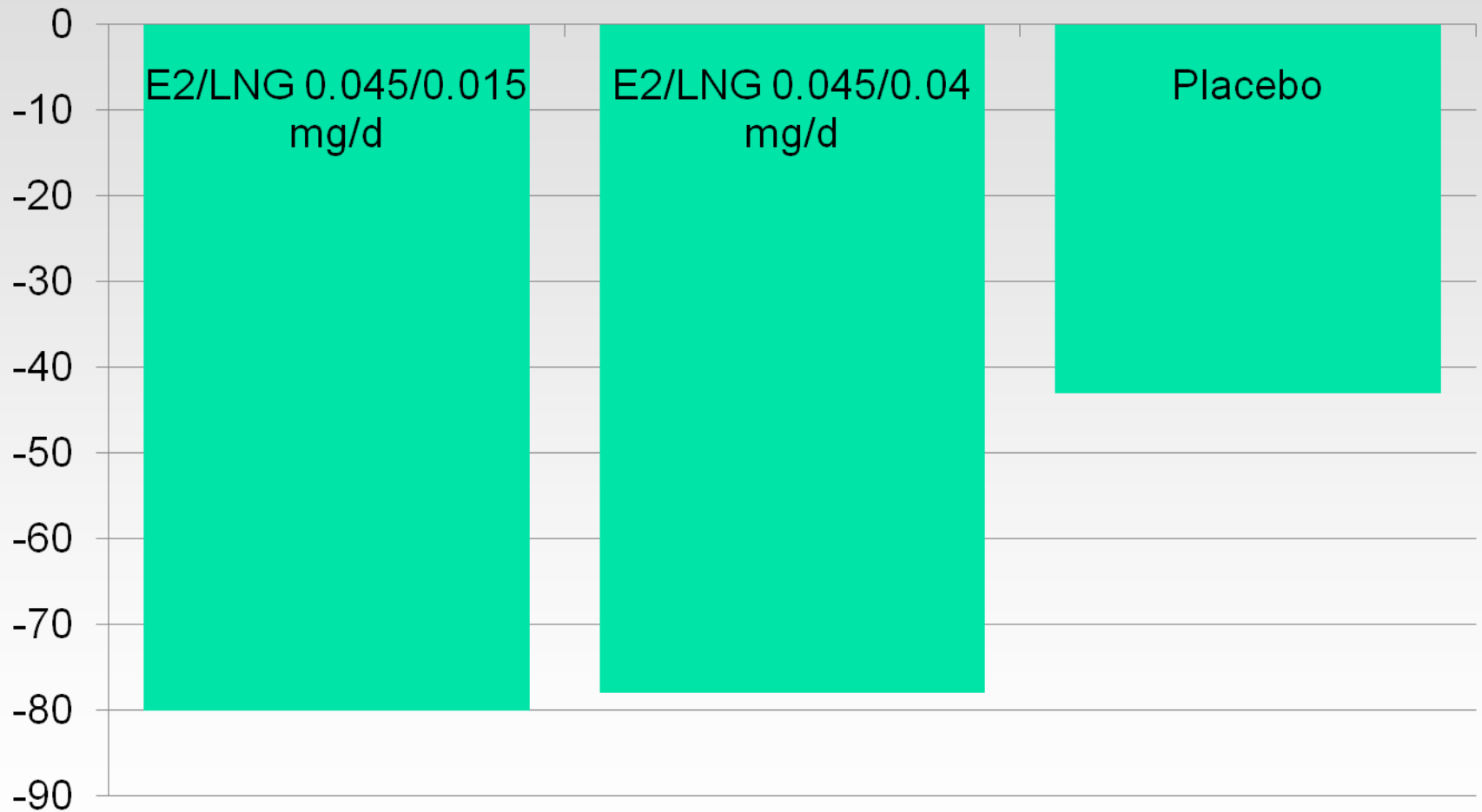


# Effect of Transdermal Estradiol and MPA on Insulin Sensitivity In Women



# Transdermal E<sub>2</sub>/LNG Treatment

Hot Flash Frequency — Change From Baseline (%)



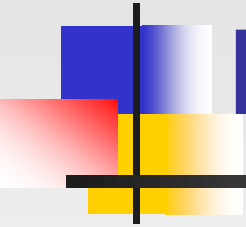
# HT Therapy and Lipid Levels

	Oral E	Oral E+P	Transdermal E	Transdermal E+P
Total cholesterol	↓	↓	↓	↓
LDL-cholesterol	↓	↓	↓	↓
HDL-cholesterol	↑	(↑)	↑	(↑)
Triglycerides	↑	(↑)	↓	↓

E+P is estrogen + progestin combination. Parentheses indicate blunted effect relative to unopposed estrogen.

# Adding Progestins: Optimizing Benefits, Minimizing Risk

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Does the type of progestin  
matter?



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# HT Use in France

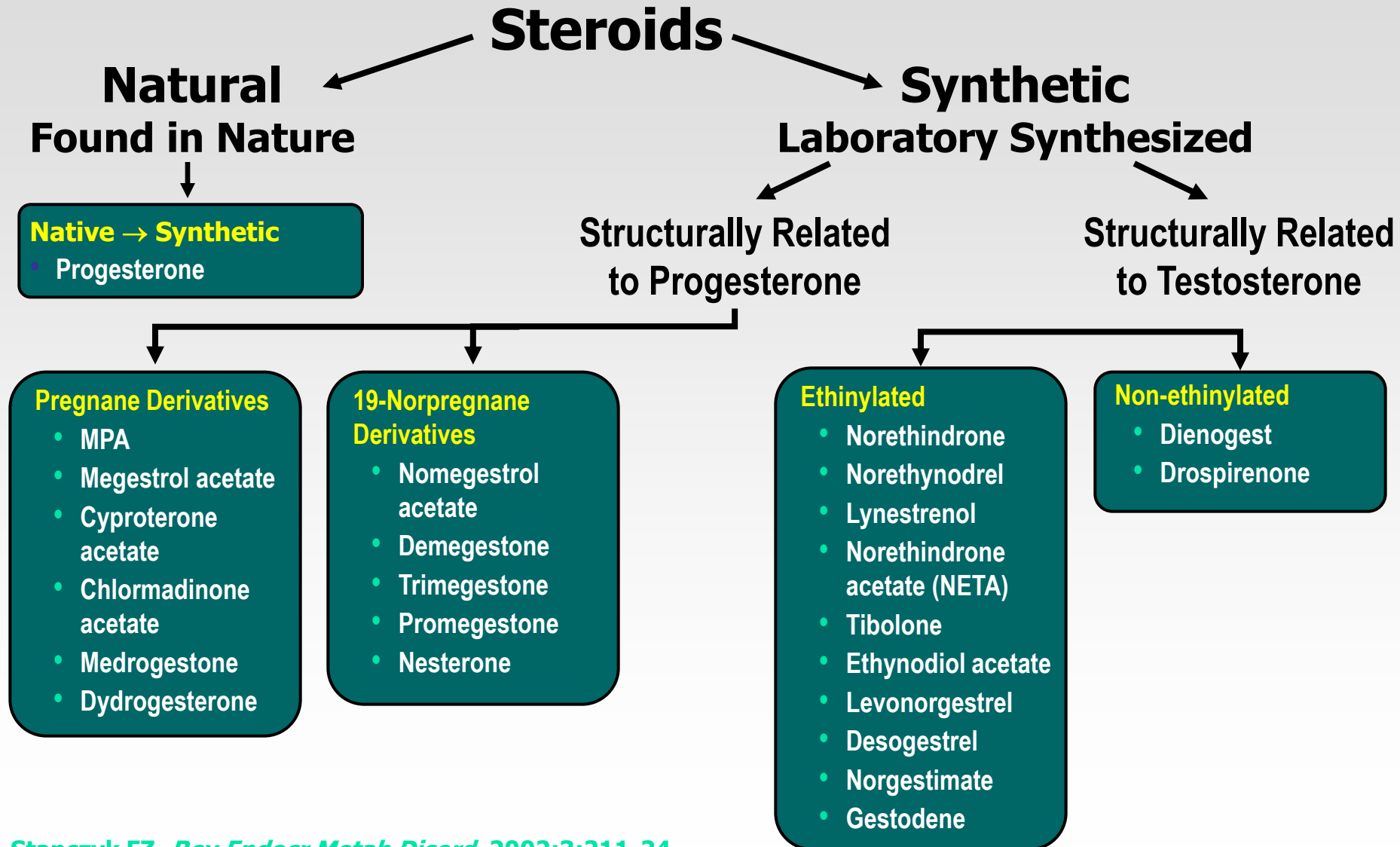
- ⑩ Transdermal estrogen~ 80%
- ⑩ French Cohort study
  - 83% transdermal estradiol gel + progestin other than MPA
- ⑩ Progestins
  - Micronized progesterone
  - Dydrogesterone
  - Chlormadinone acetate
  - Medrogestone
  - Nomegestrol acetate
  - Promegestone
- ⑩ MPA<5%, NETA<15%



# EPIC

	RR [95% CI]	
Estrogen alone	RR = 1.1 [0.8-1.6]	
<b>TRANSDERMAL ESTROGENS</b>		
With micronized progesterone	RR = 0.9 [0.7-1.2]	cases = 55
With oral synthetic progestins	RR = 1.4 [1.2-1.7]	cases =187
<b>ORAL ESTROGENS</b>		
With oral synthetic progestins	RR = 1.5 [1.1-1.9]	cases = 80

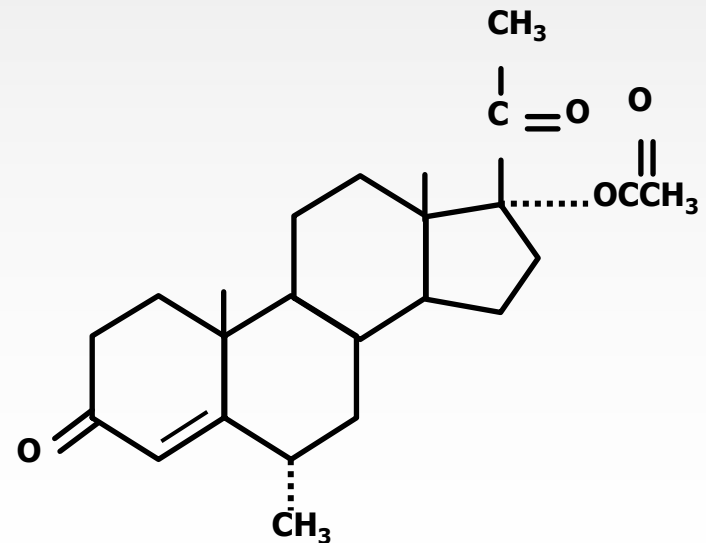
# Progestins





# Medroxyprogesterone Acetate

- ⑩ Most common progestin used in USA
- ⑩ Most intensely studied progestin
- ⑩ Only progestin with substantial data proving ability to prevent endometrial cancer long term<sup>1</sup>
- ⑩ Challenges regarding cardiac effects

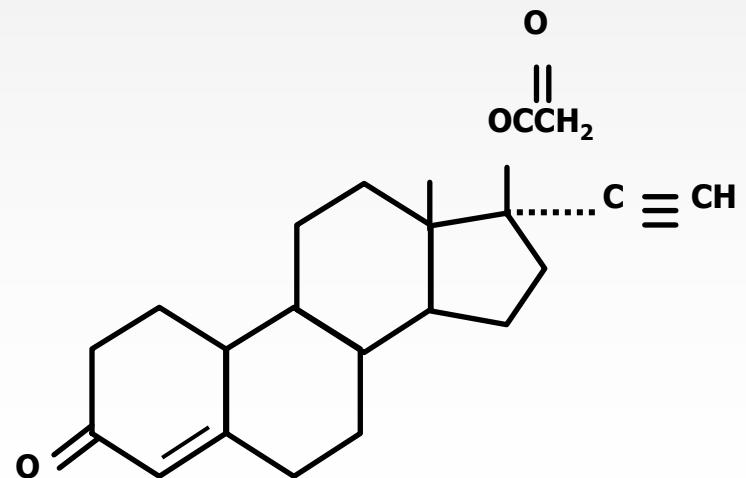


# Norethindrone Acetate

- ⑩ Synthetic, patented in 1950
  - Pro-drug, rapidly converted to norethindrone
  - First 24 hours NET > NETA,
  - 24-48 hours equilibrium, 72 hours NETA 1.5 > NET
  - NETA long half life

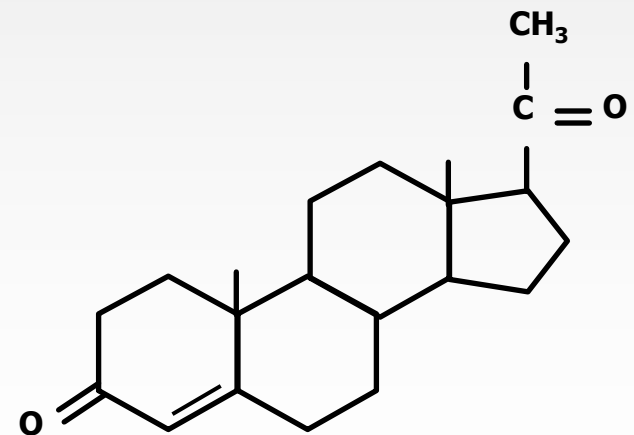
- ⑩ ***Most common progestin in EU***

- NETA converts to ethinyl estradiol
- In high dose, 0.7 - 1%
- 6 micrograms EE/1 milligram NETA



# Natural Progesterone

- ⑩ Bioidentical
- ⑩ Several formulations
- ⑩ Short half life
- ⑩ No long term safety outcomes



# Absorption of Progesterone Formulations

PROGESTERONE FORMULATION	Mean Peak Level	Hours to Peak Post Administration
Plain milled	9.6 +/- 2.5 ng/ml	4.0 +/- 0.5
Micronized	13.2 +/- 2.4 ng/ml	3.2 +/- 0.4
Micronized in oil	30.3 +/- 7.0 ng/ml	2.0 +/- 0.3
Micronized in enteric coated capsule	11.2 +/- 3.0 ng/ml	4.1 +/- 0.7

Hargrove JT, Maxson WS, Wentz AC. Absorption of oral progesterone is influenced by vehicle and particle size. *Am J Obstet Gynecol.* 1989;161:948-951.

# PEPI Treatment Arms

## ⑩ Regimens

- CEE, 0.625 mg daily
  - Plus MPA, 2.5 mg daily
  - Plus MPA, 10 mg 12 d/mo
  - Plus micronized P, 200 mg 12d/mo
  - Placebo
- 
- ⑩ First large clinical trial comparing progesterone to a synthetic progestin

# Depression and Progestins

- ⑩ 23 early postmenopausal women
  - (average age, 52.5 years) 91-day pilot study
  - 2 weeks 0.625 mg CEE
  - 2 weeks of CEE plus progestogen
  - 2 weeks of CEE
  - 2 weeks of CEE plus progestogen.
- ⑩ MPA (5 mg/day) vs micronized progesterone in oil (200 mg/day)
- ⑩ *MPA users had more vaginal bleeding and breast tenderness*

***BUT...***

# Espirit: Estrogens

Who is stronger, who is weaker?





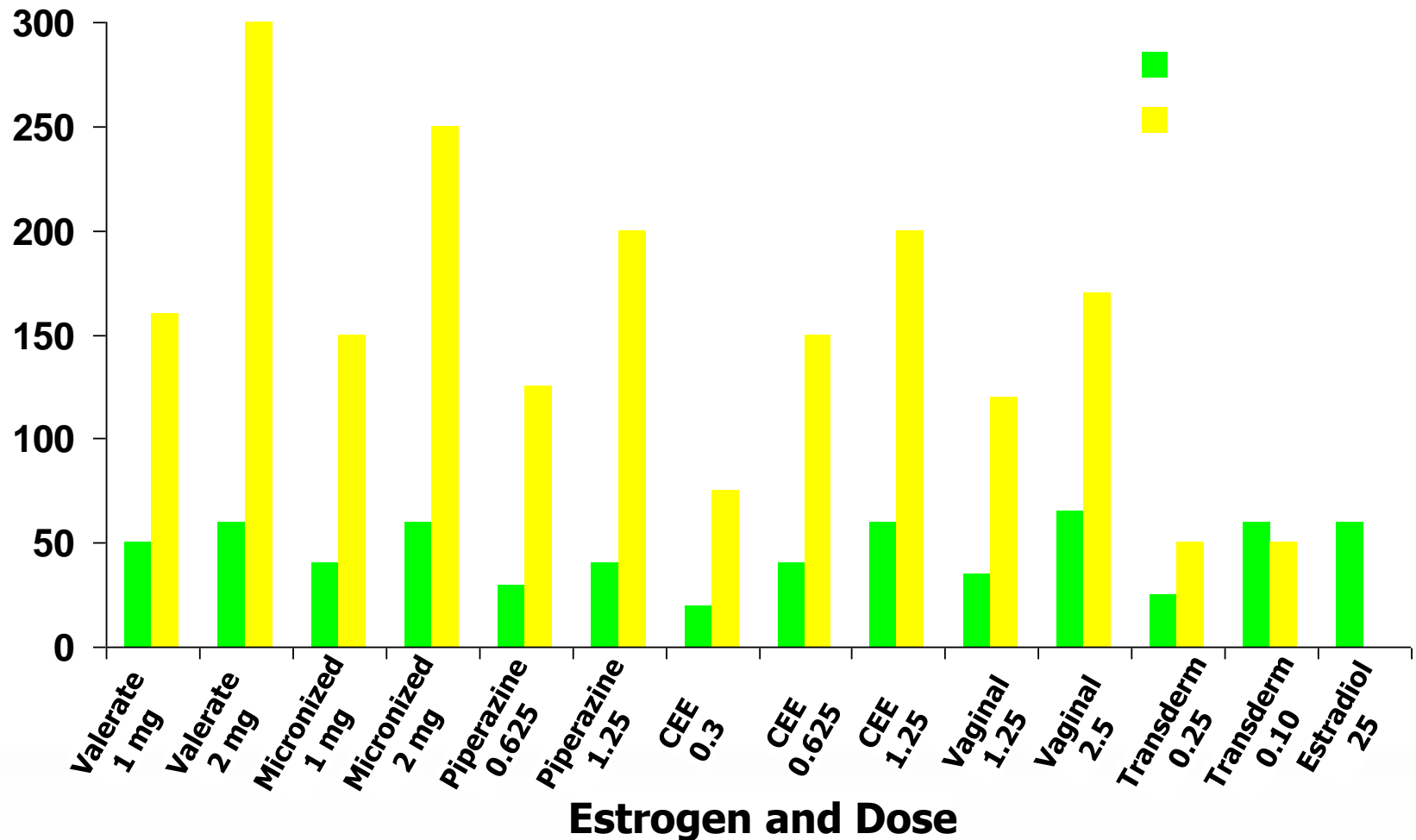


# Optimal Dose of Estradiol

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**Depends on the target  
tissue**

# Serum Estrone and Estradiol Levels After Various Doses of Estrogen Replacement



# Low Dose? Really?

- ⑩ CEE 0.45 mg
  - 25% reduction total dose
  - estimated to yield serum estradiol  $\approx$  30 pg
  - CEE 0.45 mg = E2 1 mg
  - ***BUT...***
- ⑩ again delta 8,9 has to be factored in
  - 18% higher bioactivity
  - CEE 0.45 mg should be approximately 18% more active than E2 1 mg

# Low Dose? Really?

- 10 CEE 0.3 mg
  - serum E2 = 18 pg /ml
  - but again must addback 18% for the delta 8,9 dehydroestrone activity
  - 0.3 mg would still then be lower than E2 1 mg with
  - bio activity  $\approx$  30% lower than E2 1 mg

# Estrogen Dose Stratification

Premarin 0.625 mg

Premarin 0.45 mg

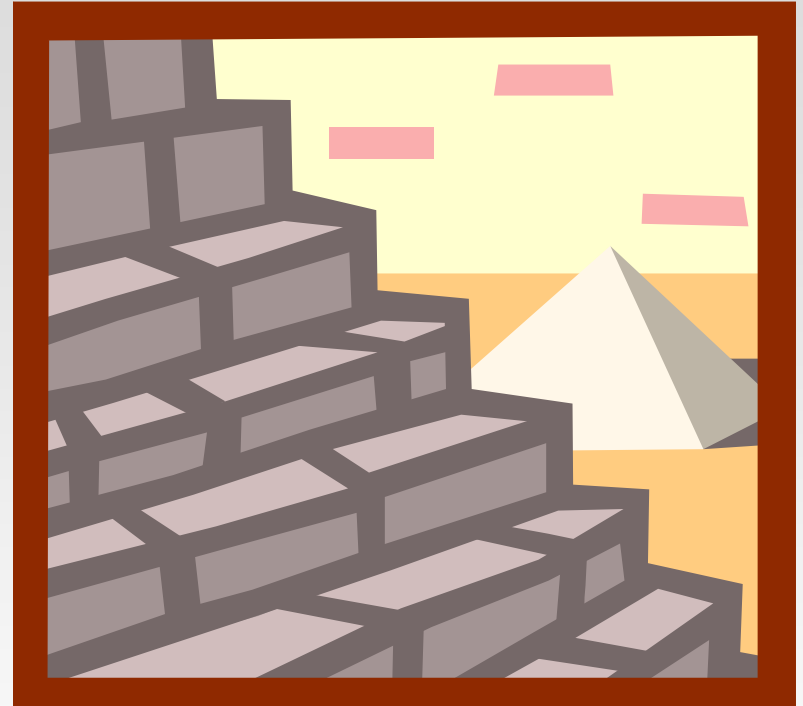
Estradiol 1 mg/ TD 0.050 mcg

Ethinyl estradiol 5 mcg

Premarin 0. 3 mg

Estradiol 0.5 mg/TD 0.025 mcg

Ethinyl estradiol 2.5 mcg



# Estrogens: Natural Versus Synthetic

## Natural Found in Nature

### Natural Source

No chemical modifications

- Conjugated equine estrogen (CEE)

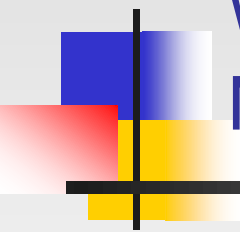
### Native → Synthetic

Biosynthetic from diosgenin

- 17 $\beta$ -estradiol
- Estrone
- Estrone sulfate
- Synthetic conjugated estrogens
- Esterified estrogens

## Synthetic Laboratory Synthesized

- Ethinyl estradiol
- Diethylstilbestrol
- Dienestrol



Will the lowest effective dose of estrogen carry  
NO endometrial cancer risk?

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10 Studies pending. Risk will trend towards zero



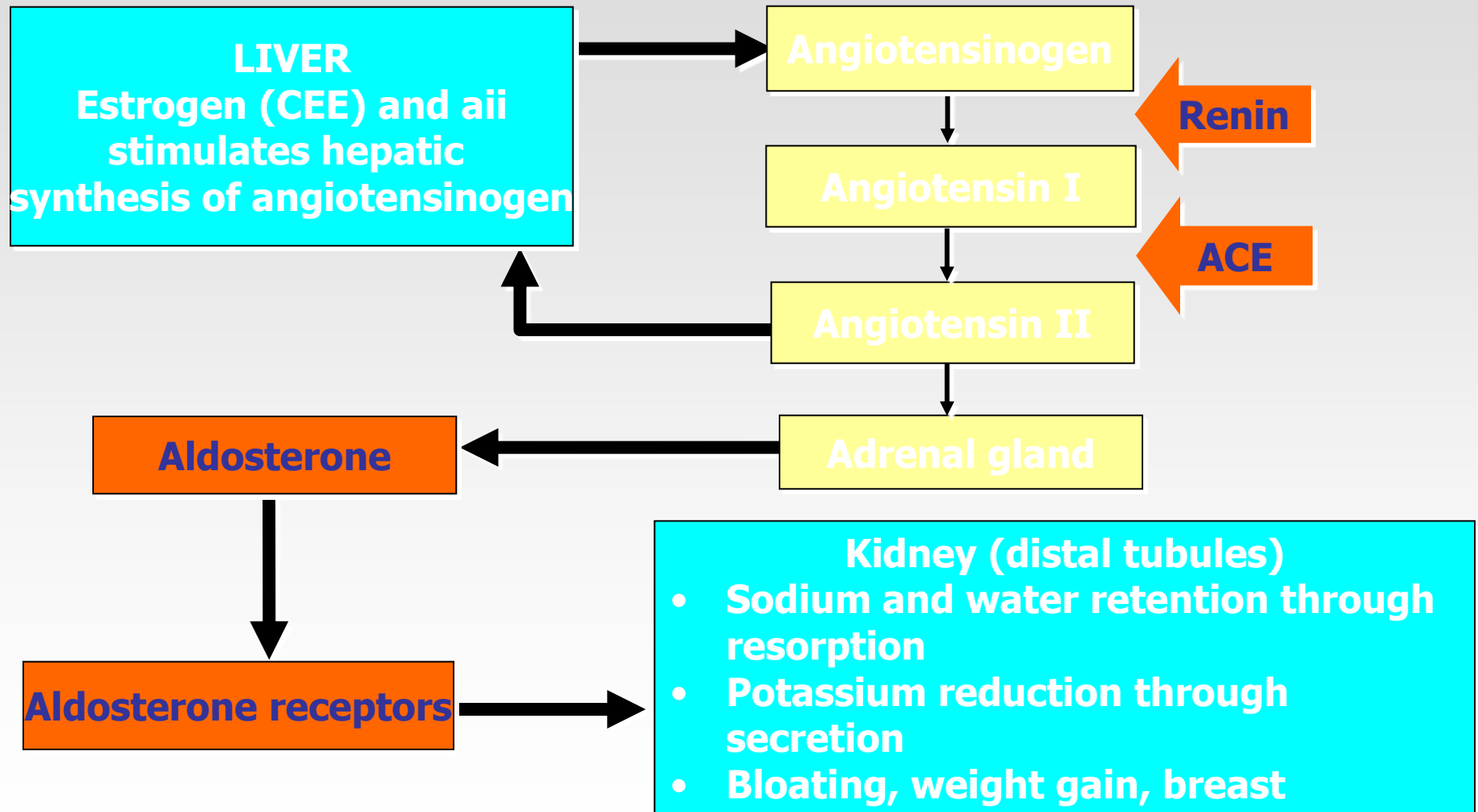
# Metabolic Risks and Benefits

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- ⑩ Cardiovascular markers
- ⑩ Inflammatory proteins
- ⑩ Glucose metabolism



# Renin-Angiotensin-Aldosterone System (RAAS)





# Coagulation markers

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⑩ CEE

⑩ E2

⑩ Esterified Estrogens

# Esterified Estrogens vs CEE and MI and Stroke

- ⑩ Same data set
- ⑩ MI or stroke with CEE or EE comparable
- ⑩ Restricting to hormone users only, suggestion of higher ischemic stroke risk with CEE alone (without progestin) compared with EE alone
  - (OR 1.57; 95% confidence interval, 0.98-2.53).
- ⑩ suggestion that when initiated in previous 6 months, CEE associated with higher risk of MI than EE
  - (odds ratio, 2.33; 95% confidence interval, 0.93-5.82)

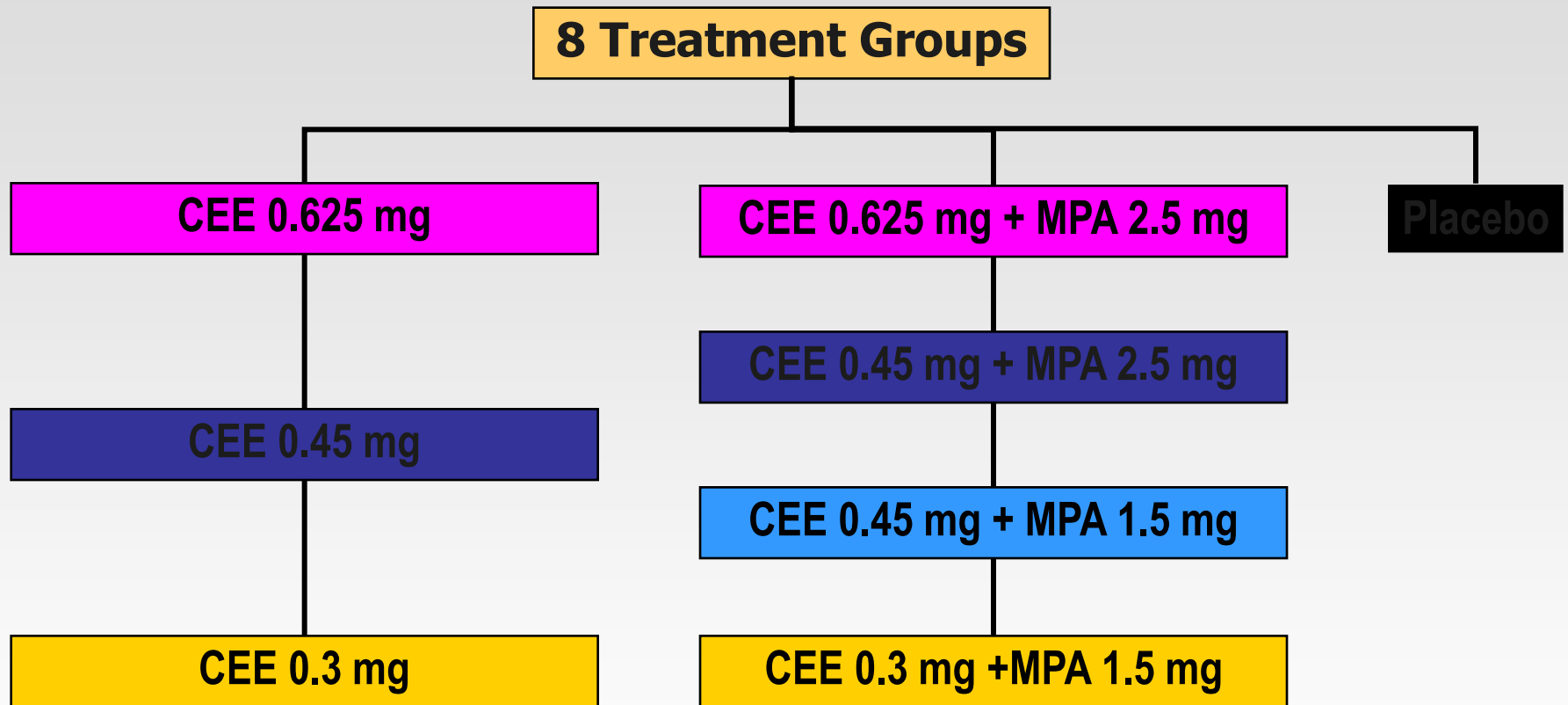
# Prempro lower doses: Pivotal Studies



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 HOPE

# Women's HOPE Study



A double-blind, double-dummy design was used to administer study medication.  
All groups received a calcium carbonate supplement (600 mg elemental calcium/day).  
Utian WH, et al. *Fertil Steril*. 2001;75:1065-79.

# Prempro lower dose messaging

- Research findings demonstrate that lower doses of estrogen and progestin
  - Relieve vasomotor symptoms and prevent vaginal atrophy
  - Are associated with a reduced incidence of endometrial bleeding, especially in the early months of therapy
  - Provide effective endometrial protection
  - Prevent early postmenopausal bone loss
- Lower-dose regimens provide clinicians and patients with expanded options for individualizing HT
- E alone at lower dosages for longer durations may be associated with increased rates of endometrial hyperplasia



# Tibolone



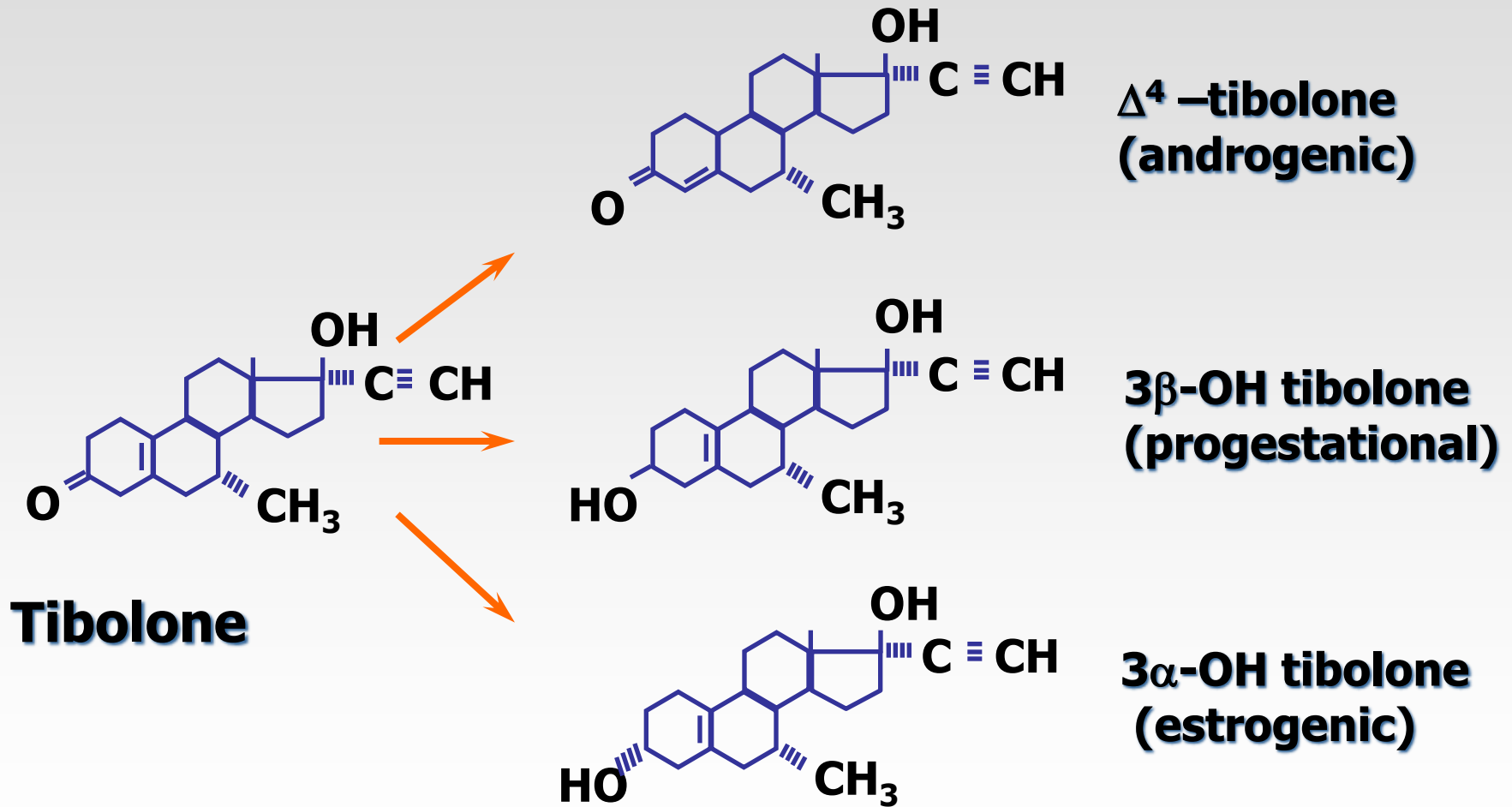
- ⑩ Livial in EU, AU etc
- ⑩ (Zyvion in USA)

# Tibolone

- ⑩ characterized as a selective tissue estrogenic activity regulator or STEAR
- ⑩ norethindrone analogue
- ⑩ dose ranges
  - VMF 2.5 mg
  - Libido 5 mg
  - Bone 1.5 mg (anticipated dose for USA)
- ⑩ Long term safety data have been lacking
- ⑩ before 2000, few quality clinical trials

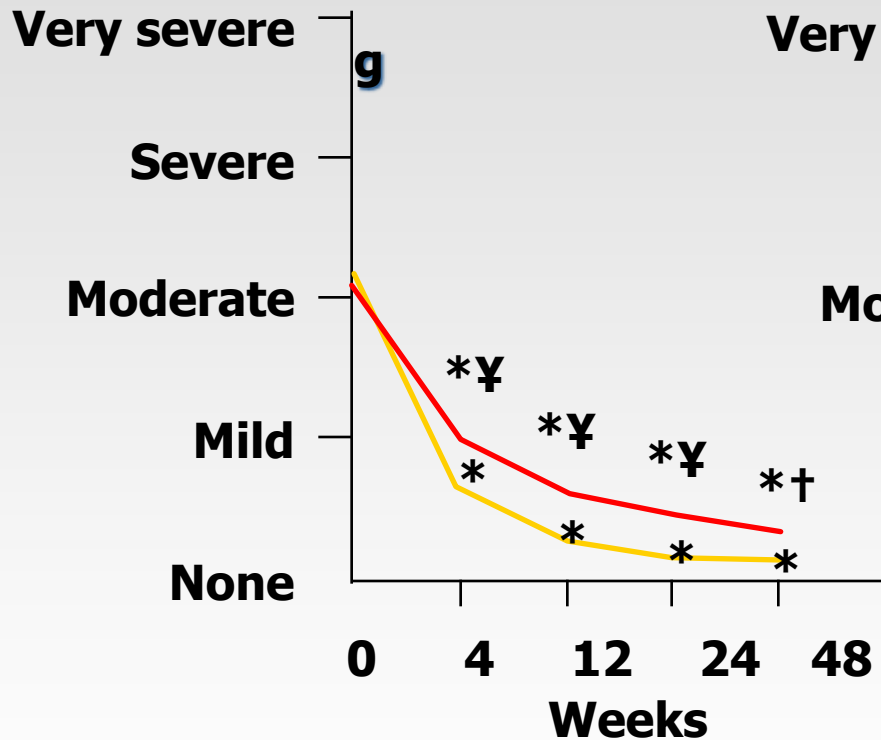


# Metabolic Conversion of Tibolone

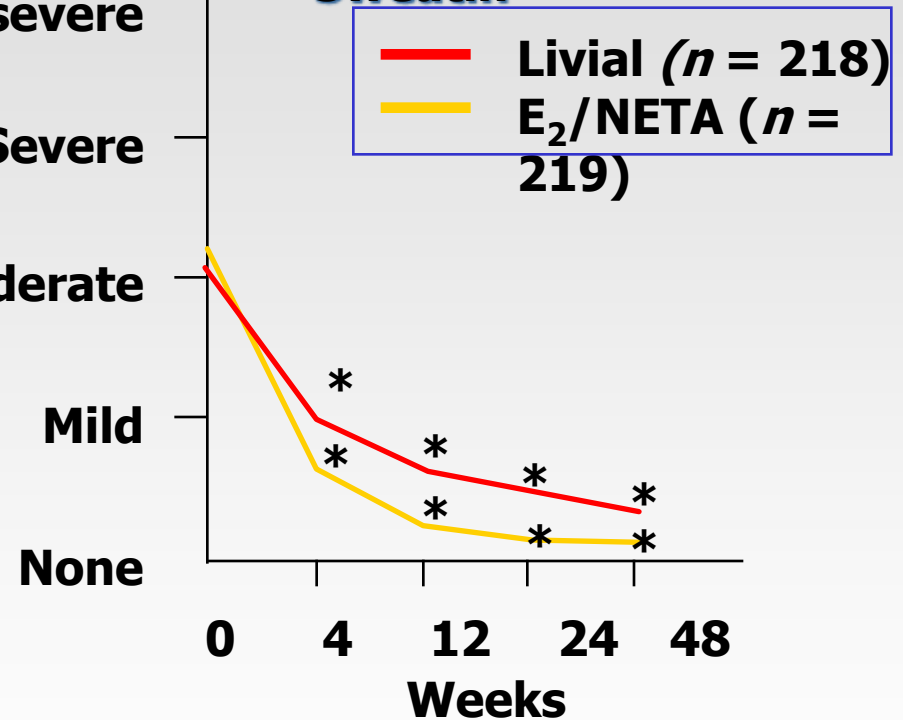


# Livial<sup>®</sup>: Hot Flashes and Sweating

## Hot flushes



## Sweatin

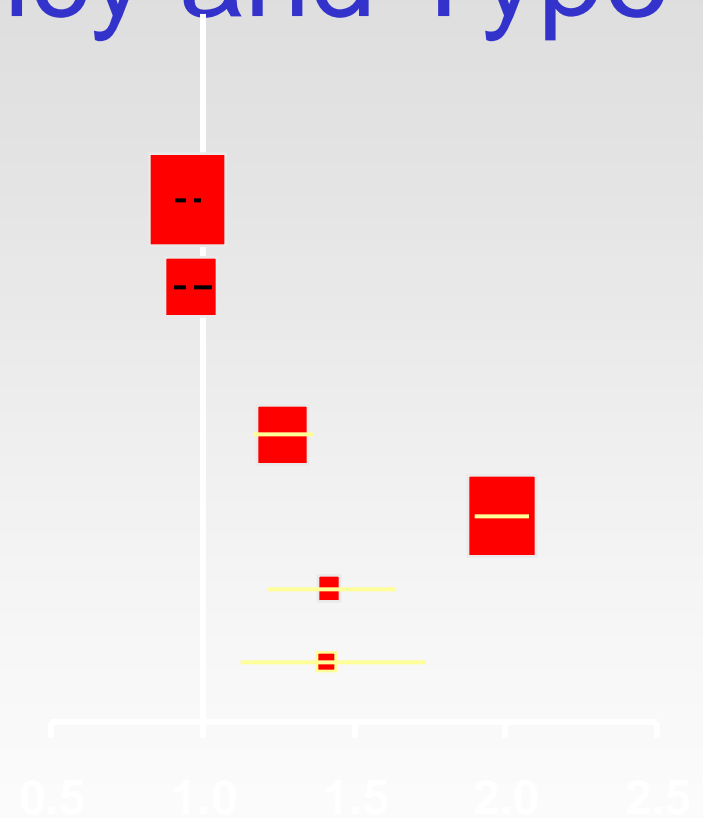


E<sub>2</sub>/NETA, 17 $\beta$ -estradiol (2mg/day)/norethisterone acetate (1 mg/day)

\*  $p < 0.001$  vs. baseline †  $p < 0.01$ ; ‡  $p < 0.001$  between groups

# Incident Invasive Breast Cancer in Relation to Recency and Type of HT Used

HT Use at Baseline	Relative Risk (95% FCI)*
<i>All never-users</i>	1.00 (0.96–1.04)
<i>All past users</i>	1.01 (0.95–1.08)
<i>Current users</i>	
<i>E-only</i>	1.30 (1.22–1.38)
<i>E+P</i>	2.00 (1.91–2.09)
<b><i>Tibolone</i></b>	<b>1.45 (1.25–1.67)</b>
<i>Other/unknown types</i>	1.44 (1.17–1.76)



FCI = floated CI.

\*Relative to never-users, stratified by age, time since menopause, parity and age at first birth, family history of breast cancer, body mass index, region, and deprivation index.

Million Women Study Collaborators. *Lancet*. 2003;362:419-27.

# Pending Trials of Livial:

## Countering complaints or too little too late?

- ⑩ LIFT: Long-Term Intervention on Fractures with Tibolone 4000 women over 3 yr
- ⑩ LIBERATE: Livial Intervention following Breast cancer: Efficacy, Recurrence And Tolerability Endpoints
- ⑩ THEBES: Tibolone Histology of the Endometrium and Breast Endpoints Study
- ⑩ LISA: Livial International Study in Sexual arousal disorders
- ⑩ STEP: Study of Tibolone's Effects - tibolone and raloxifene on bone mineral in osteopenia
- ⑩ TOTAL: Tolerability Trial comparing ActiVelle with Livial in climacteric symptoms, quality of life and sexual function in postmenopausal women.

# Post-WHI: Summary of ACOG, NAMS and ASRM Position Statements on HT

- ⑩ HT is effective for the relief of hot flashes
- ⑩ Use HT at lowest effective dose for the shortest possible duration
- ⑩ For osteoporosis prevention only, use alternative non-hormonal medications
- ⑩ HT should not be used for the prevention of heart disease
- ⑩ Risk of breast cancer may increase with long-term EPT
- ⑩ Risks and benefits of HT should be considered on an individual basis

ACOG, American College of Obstetricians and Gynecologists; NAMS, North American Menopause Society; ARSM, American Society for Reproductive Medicine

American College of Obstetricians and Gynecologists. *Questions and Answers on Hormone Therapy In Response to the Women's Health Initiative Study Results on Estrogen and Progestin Hormone Therapy*. Available at: <http://www.acog.org>. Accessed May 10, 2006.  
NAMS 2003 Hormone Therapy Advisory Panel. *Menopause*. 2003;10:497-506. American Society for Reproductive Medicine. Available at: <http://www.asrm.org>. Accessed May 10, 2006.

# Individualizing the Treatment Plan for Hormone Therapy

- It is important for the clinician to ascertain the patient's attitude toward menopausal transition and preference for a specific treatment, and learn about any concerns that the patient may have regarding a specific treatment option.
- It is important to integrate patient attitudes and views when formulating individualized treatment plans.

# HT and Vasomotor Symptoms

- Treatment of moderate to severe vasomotor symptoms (ie, hot flashes, night sweats) remains primary indication for systemic ET/EPT
- With few exceptions, every systemic ET/EPT product is government approved for this indication

# HT and Vaginal Atrophy

- When HT is considered solely for this indication, local (not systemic) vaginal ET is generally recommended
- Progestogen generally not indicated with low-dose, local vaginal ET



# Progestogen Indication

- Primary menopause-related indication is endometrial protection from unopposed ET
- Adequate progestogen (as CC-EPT or CS-EPT) recommended with intact uterus
- Progestogen not generally indicated with ET post-TAH

# HT and Coronary Heart Disease

- ET/EPT not recommended as single or primary indication for coronary protection in women of any age
- Data do not currently support EPT in secondary prevention of CHD

# HT and Diabetes Mellitus

- Large RCTs suggest HT reduces new DM onset
- Inadequate evidence to recommend combined EPT for sole indication of prevention of DM in perimenopausal women

# EPT and Breast Cancer Risk

- Breast cancer risk increases with EPT use beyond 5 years
- Increased absolute risk in WHI is viewed as rare (4-6 additional invasive cancers/10,000 women/yr when use EPT for  $\geq 5$  yrs)
- Not clear whether risk differs between CC-EPT and CS-EPT

(cont'd)

# ET and Breast Cancer Risk (cont'd)

- Women in WHI's ET arm had 8 fewer cases of invasive breast cancer/10,000 women/yr of ET use
- Available evidence suggests ET for <5 yr has little breast cancer risk impact
- Inadequate evidence to support any indication for ET in reduction of breast cancer risk
- Limited observational data suggest ET for >15 yr may increase risk

# HT and Breast Effects

- EPT and to a lesser extent ET increase breast cell proliferation, breast pain, mammographic density
- EPT may impede diagnostic interpretation of mammograms
- Minimal data reporting any change in breast cancer mortality with ET/EPT

# HT and Osteoporosis

- Strong evidence of ET/EPT's efficacy in reducing postmenopausal osteoporotic fracture risk
- Many ET/EPT products government approved for postmenopausal osteoporosis prevention through long-term treatment
- ET/EPT is an option for osteoporosis risk reduction (including women at high risk of fracture during the next 5-10 yr), weighing its risks/benefits as well as those of other government-approved products

# HT and Cognition

- Initiating EPT after age 65 not recommended for primary prevention of dementia or cognitive decline
- Insufficient evidence to support ET/EPT for primary prevention of dementia when therapy is initiated during perimenopause or early postmenopause
- ET does not appear to convey direct benefit or harm for treatment of Alzheimer's disease



# HT and Premature Menopause

- Premature menopause and premature ovarian failure are associated with lower risk of breast cancer and earlier onset of osteoporosis and CHD
- No clear data as to whether ET or EPT will affect morbidity or mortality from these conditions
- Risk-benefit ratio for younger women who initiate therapy at an early age may be more favorable, but is currently unknown

# Risk-Benefit Ratio Important

Use of ET/EPT should be consistent with treatment goals, benefits, and risks for the individual woman, taking into account:

- Cause of menopause
- Time since menopause
- Symptoms
- Domains (eg, sexuality, sleep) that may affect quality of life and underlying risk of CVD, stroke, VTE, DM, and other conditions

# Lower HT Doses

- Provide nearly equivalent vasomotor and vulvovaginal symptom relief and preservation of bone mineral density to standard doses
- Additional local ET may be required for persistent vaginal symptoms
- Lower HT doses are better tolerated and may have a better risk-benefit ratio than standard doses
- However, lower doses have not been tested in long-term trials

(cont'd)

# Lower HT Doses (cont'd)

Lower than standard ET/EPT doses should be considered, such as daily doses of:

- 0.3 mg oral conjugated estrogens
- 0.25-0.5 mg oral micronized  $17\beta$ -estradiol
- 0.025 mg transdermal  $17\beta$ -estradiol patch
- or the equivalent

# Caution When Extrapolating Data

- ET/EPT effects on risk of breast cancer, CHD, stroke, total CVD, and osteoporotic fracture in perimenopausal women with moderate to severe menopause symptoms have not been established in RCTs
- Thus, findings from trials in different populations should be extrapolated with caution

# Extended Low-Dose HT

Acceptable under the following circumstances, provided the woman is well aware of potential risks and benefits and that there is clinical supervision:

- For the woman for whom, in her own opinion, the benefits of menopause symptom relief outweigh risks, notably after failing an attempt to stop HT

(cont'd)

# Extended Low-Dose HT (con'd)

- For women who are at high risk for osteoporotic fracture and also have moderate to severe menopause symptoms
- For further prevention of bone loss in women with established reduction in bone mass when alternate therapies are not appropriate for that woman, cause side effects, or when the outcomes of the extended use of alternate therapies are unknown

# HT and Quality of Life

- Improved health-related quality of life (HQOL) can result with HT through decreased menopause symptoms and possible elevation of mood that lead to a feeling of well-being
- Lack of consensus on the impact of HT on overall QOL and HQOL in asymptomatic women
- Validated instruments for determining the impact of HT and any menopause-related therapy on overall QOL and HQOL should be incorporated into future studies



# Areas of Nonconsensus

- What is the best way to discontinue HT?
- Are the effects of CC-EPT different from CS-EPT?

# Summary

- For women suffering severe menopausal symptoms, systemic HT benefits generally outweigh risks.
- It is currently not appropriate to prescribe systemic HT for the sole indication of prevention of heart disease.
- Change continues — keep an open mind.